Use of Partial Area Under the Curve for BE Assessment of Products with Complex PK Profiles; a View Point

Kamal K. Midha
Gordon McKay

University of Saskatchewan
and Pharmalytics Ltd.
CANADA

Presentation to USFDA
2010, Washington, DC

Declaration of Interests

The following presentation reflects the views of the authors and does not represent the opinion or influence of any other agency, corporation or individuals.

Author (KKM) is currently President of FIP, a not-for-profit professional and scientific international federation, declares current or past (18 months) consulting relations with Solvay, Wyeth, TEVA, Sanofi Aventis, Dexon and Daichi Sankyo totalling no more than 5% of the author's time spent on consulting with the above on an ad hoc basis.

Author (GM) is currently CEO of Pharmalytics Ltd., a CRO which provides scientific services to both generic and brand pharmaceutical firms.

Modified-Release Products

- Modified-release (MR) drug products are complex dosage forms designed to release drug in a controlled manner to achieve desired efficacy and safety profiles. Also adds to convenience over immediate release (IR) products.

- According to the U.S. Food and Drug Administration (FDA) and U.S. Pharmacopeia (USP), MR solid oral dosage forms comprise delayed and extended release drug products.

- In addition to the delayed and/or prolonged release characteristics, newer oral MR products also exhibit pulsatile-release, chrono-release or targeted delivery (e.g., colonic delivery).

Adopted from M-L. Chen et al, Workshop Summary Report; Modified Release Products, AAPS/FIP, Oct. 2009, Baltimore MD

Modified-Release Products

- Moreover, some of the oral MR products in the marketplace include combinations of IR, delayed release, and/or extended release components.
- These dosage forms may be designed to deliver drugs in a controlled and predictable manner over a period of time or at a predetermined position in the gastrointestinal (GI) tract to achieve the desired therapeutic effect.
- Advances in pharmaceutical sciences have produced drug delivery systems such as novel MR dosage forms to achieve optimal target product profiles.

Adopted from M-L. Chen et al, Workshop Summary Report; Modified Release Products, AAPS/FIP, Oct. 2009, Baltimore MD

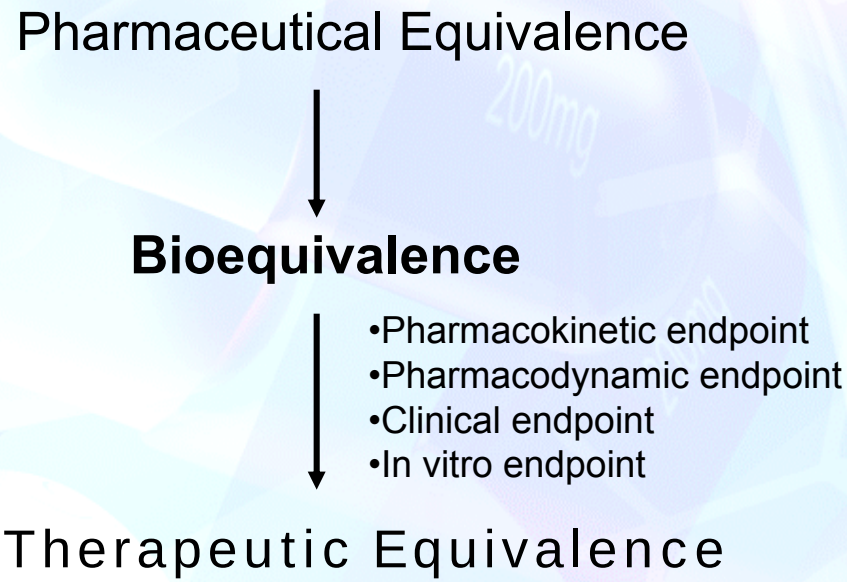
MR Product Challenges

- Given the unique features and complexities of these products, challenges are being experienced by industry and regulatory scientists in ensuring pharmaceutical equivalence, bioequivalence and therapeutic equivalence.

- Concerns in inappropriate control of drug release from such products may result in efficacy issues (reduced) or increased toxicity in drug product switchability.

- Hence our discussions and meeting today.

Drug Product Interchangeability Equivalence Concept (U.S. FDA)



- Bioequivalence is a surrogate for therapeutic equivalence
- Focus is on the documentation of bioequivalence by scientifically appropriate pharmacokinetic endpoint(s) (in majority of drug products)

Pharmaceutical Equivalents

- In the U.S., pharmaceutical equivalents are referred to drug products in **identical dosage forms** that contain **identical amounts** of the **identical active drug ingredient**, and **meet the identical or compendial or other applicable standard of identity, strength, quality, and purity, including potency** and, where applicable, content uniformity, disintegration times, and/or dissolution rates (1).
- Pharmaceutically equivalent drug products **need not contain the same inactive ingredients** and they may **differ in their** characteristics such as **shape, scoring configuration, release mechanisms, packaging, excipients** (including colors, flavors, preservatives), **expiration dates/time**, **minor aspects of labeling** (e.g., the presence of specific pharmacokinetic information) and storage conditions (2).

1. **U.S. Food and Drug Administration, Title 21 Code of Federal Regulations (CFR) Part 320.1, Office of Federal Register, National Archives and Records Administration, U.S. Government Printing Office, Washington, DC, 2009.**
2. **Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Office of Generic Drugs. Current through January 2010. http://www.fda.gov/cder/ob/default.htm. Accessed 26 Feb 2010**

Current FDA Regulatory Recommendations for MR (DR and CR/ER) Products – BA/BE Studies

- NDAs: New Drugs
  - A single dose fasting study on the highest strength
  - A single dose fed study on the highest strength
  - A steady-state study on the highest strength

- ANDAs: Generic Drugs
  - A single dose comparative non-replicate (except for HVD/P replicate design), fasting study on the highest strength
  - A single dose comparative non-replicate fed study on the highest strength

A comparative steady state study not recommended

(General Bioavailability and Bioequivalence Guidance, CDER, U.S. FDA, 1999, as revised in 2003)

Conventional Current Regulatory Recommendation for BE Studies

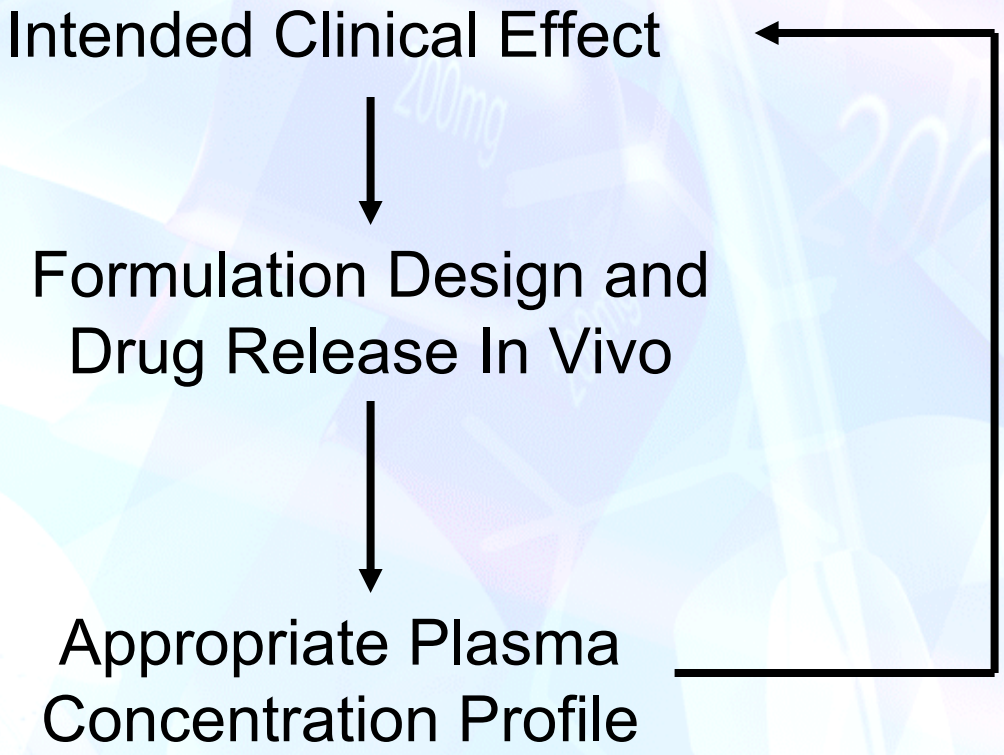
- Work well with drugs that demonstrate uncomplicated monophasic or pseudomonophasic MR drug products
- MR drugs for which rapid onset is not clinically important
- Hence present approaches and acceptance criteria are approriate for BE and therapeutic interchangability for monophasic release MR products

Drugs for which rapidity of onset is not clinically important

- Drugs with slow onset of action seem to have little possibility to produce differential efficacy/effectiveness based on differences in Tmax or shape of the plasma concentration-time profile.
- Therefore present BE assessment criteria based on Cmax, $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and Tmax are adequate because small differences in rate and peak exposure may have no serious consequences in terms of clinical efficacy and safety. Most commonly these drugs take days or weeks to illicit and achieve optimal efficacy,

  antidepressants (e.g., bupropion), antipsychotics, platelet inhibitors, lipid-lowering agents, most tumor-necrosis-factor (TNF) blockers

Design of MR Formulations: Therapeutic Considerations



Potential Considerations for BE Assessment As Surrogate for Therapeutic Equivalence of MR Drug Products

- With the present regulatory criteria many MR formulations with conventional drug release profiles *in-vivo* may be adequately addressed
- All MR products including those with other drug release profiles have been approved on the basis of acceptable safety and efficacy
- However, for some MR drug products with different drug release mechanisms, these regulatory recommendations may not be adequate
- Furthermore from clinical considerations, some drugs will exhibit efficacy on single doses (e.g., acute pain, ADHD, sleep disorder), where as other drugs (e.g., antidepressants ,antipsychotic agents) require repeated administration, sometimes for weeks before any efficacy ensues

FDA Regulatory Recommendations for MR (DR and CR/ER) Products – BE Studies

- Pharmacokinetic Information & BE Measures
  - Plasma concentrations at appropriate times
  - AUC(0-t), AUC(0-inf), Cmax, Tmax, kel, t1/2
  - Cmin, Cavg, degree of fluctuation, swing (steady state study)
  - Inter-subject, intra-subject, and/or total variability
  - ANOVA treatment,Subject, period, sequence, treatment
  - Partial AUC, (e.g. Ambien® CR)

(General Bioavailability and Bioequivalence Guidance, CDER, U.S. FDA, 1999, as revised in 2003)

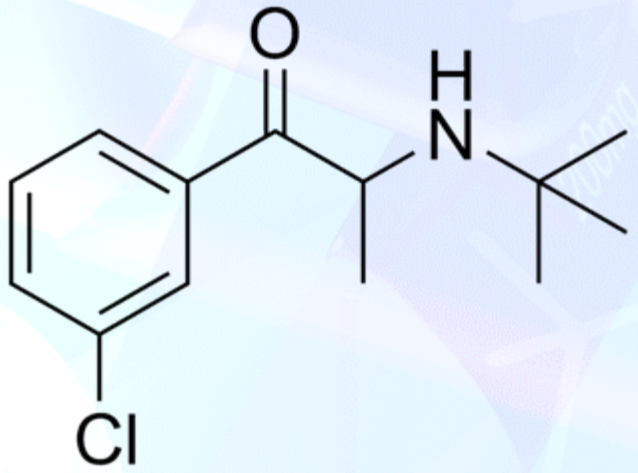
Potential Considerations for BE Assessment As Surrogate for Therapeutic Equivalence of ER Drug Products

- Recently U.S. FDA has issued a Regulatory draft BE guidance on Zolpidem tartrate Extended Release Tablet (Ambien CR) where ***Partial AUC*** (AUCp) has been added as an additional metric for BE documentation

- However, within-subject variability (WSV) of the AUCp should be carefully evaluated for recommending statistical BE limits (90% confidence interval) for this metric

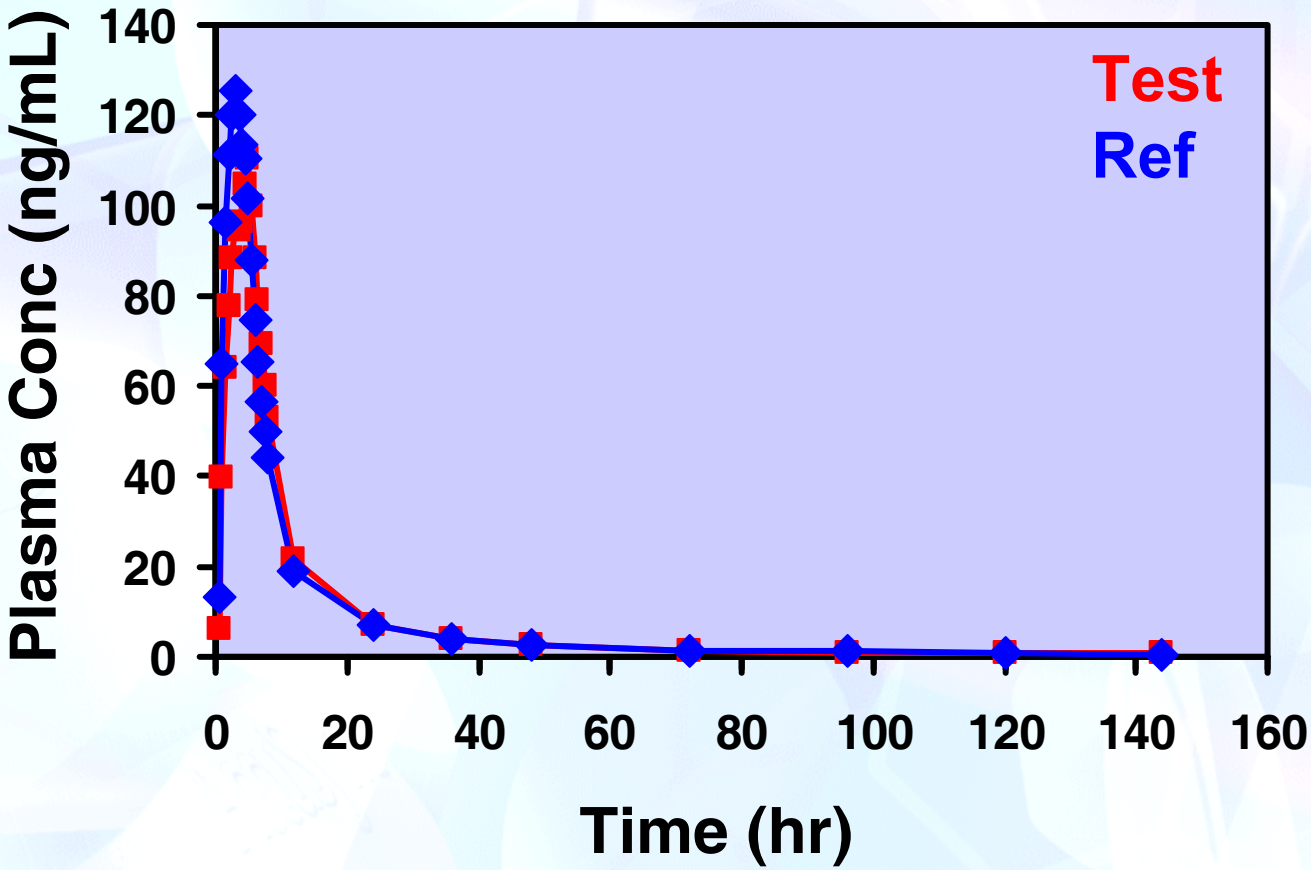
- Evaluation of AUCp and associated variability in this metric are exemplified for the following slides from actual experimental studies:
  - Bupropion SR formulation

Examples of the WSV Associated with AUCp Assessment



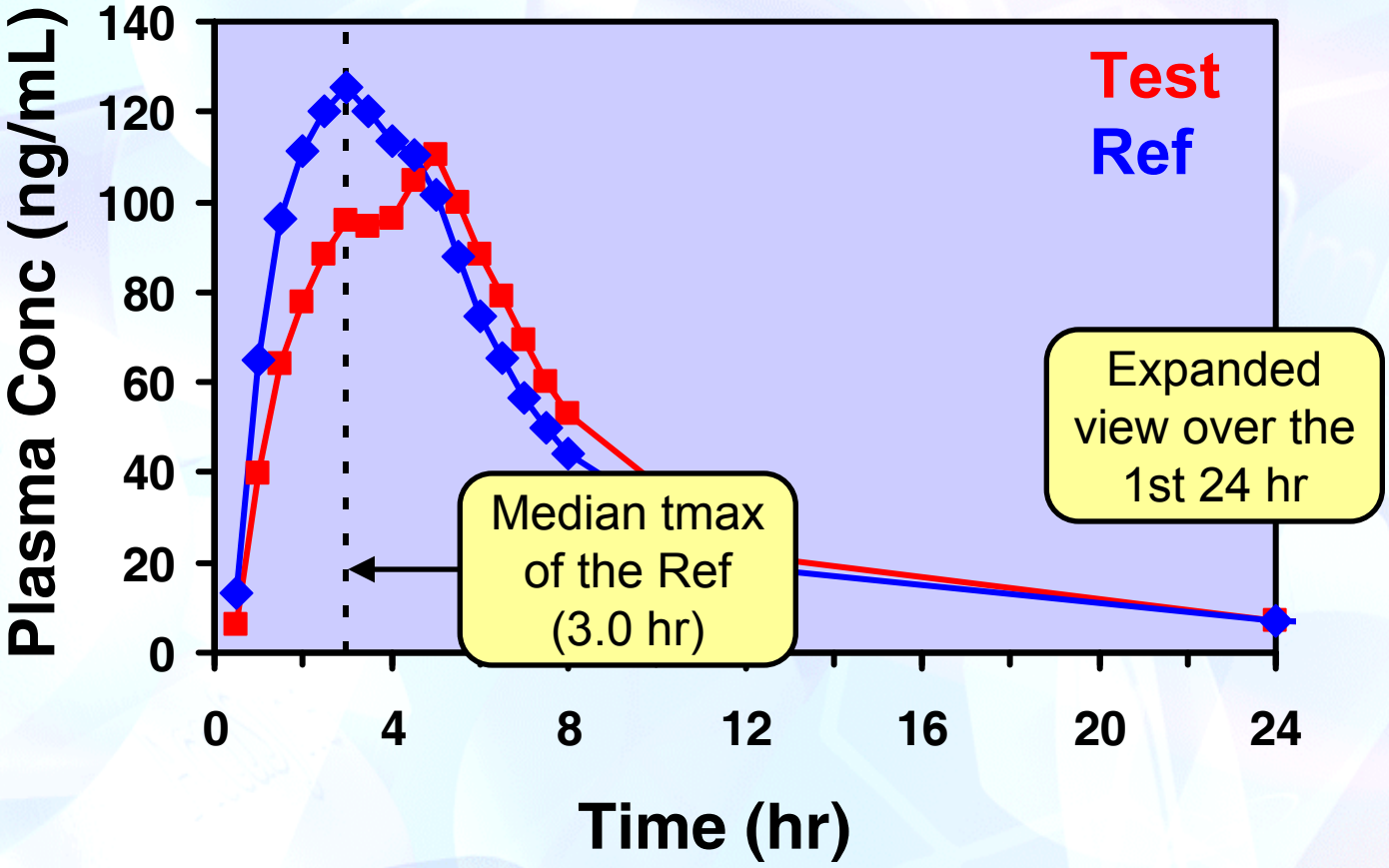
Bupropion

Bupropion SR Formulation, 150 mg

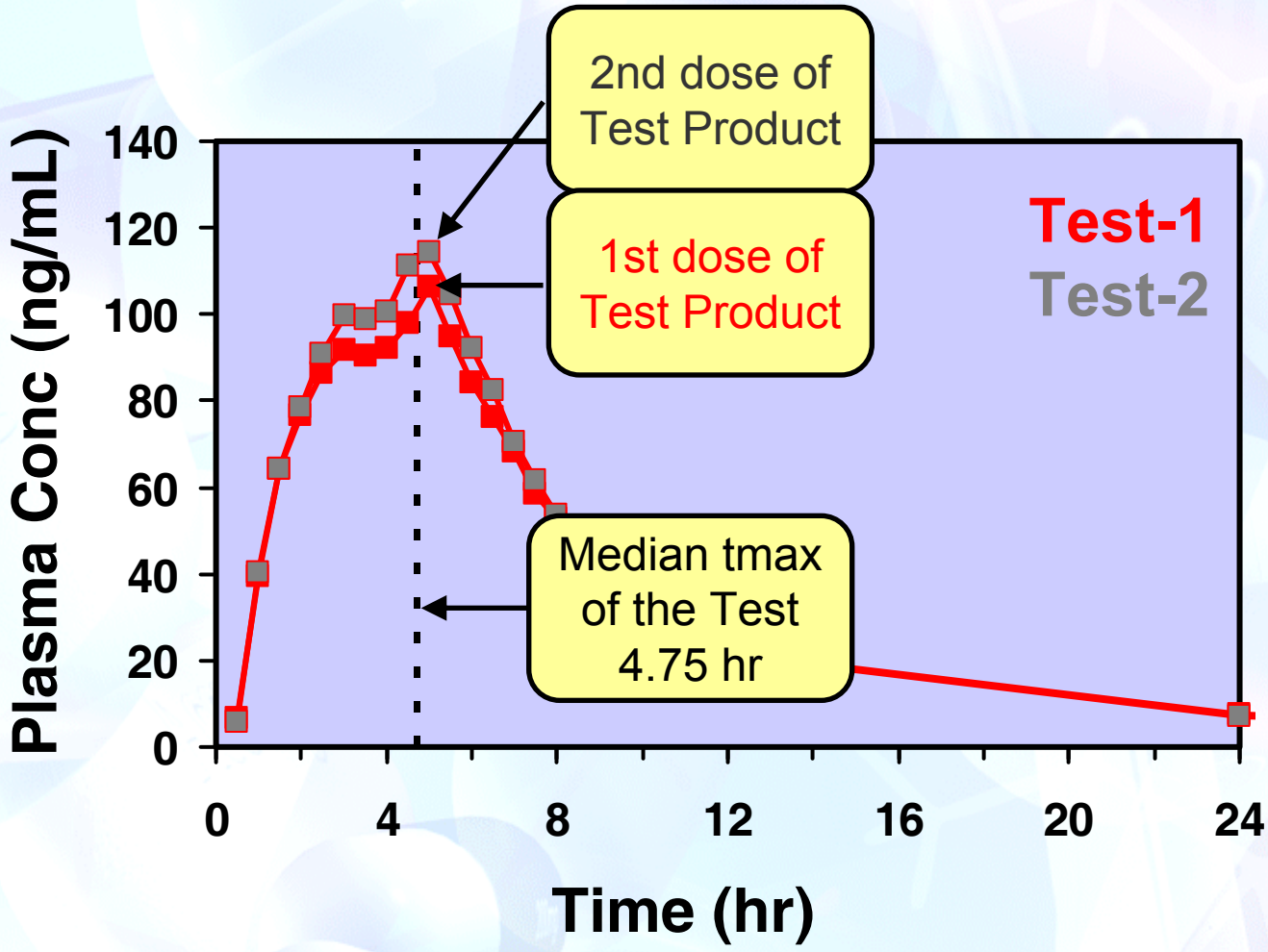


Single dose fasted, replicate design (N=29)

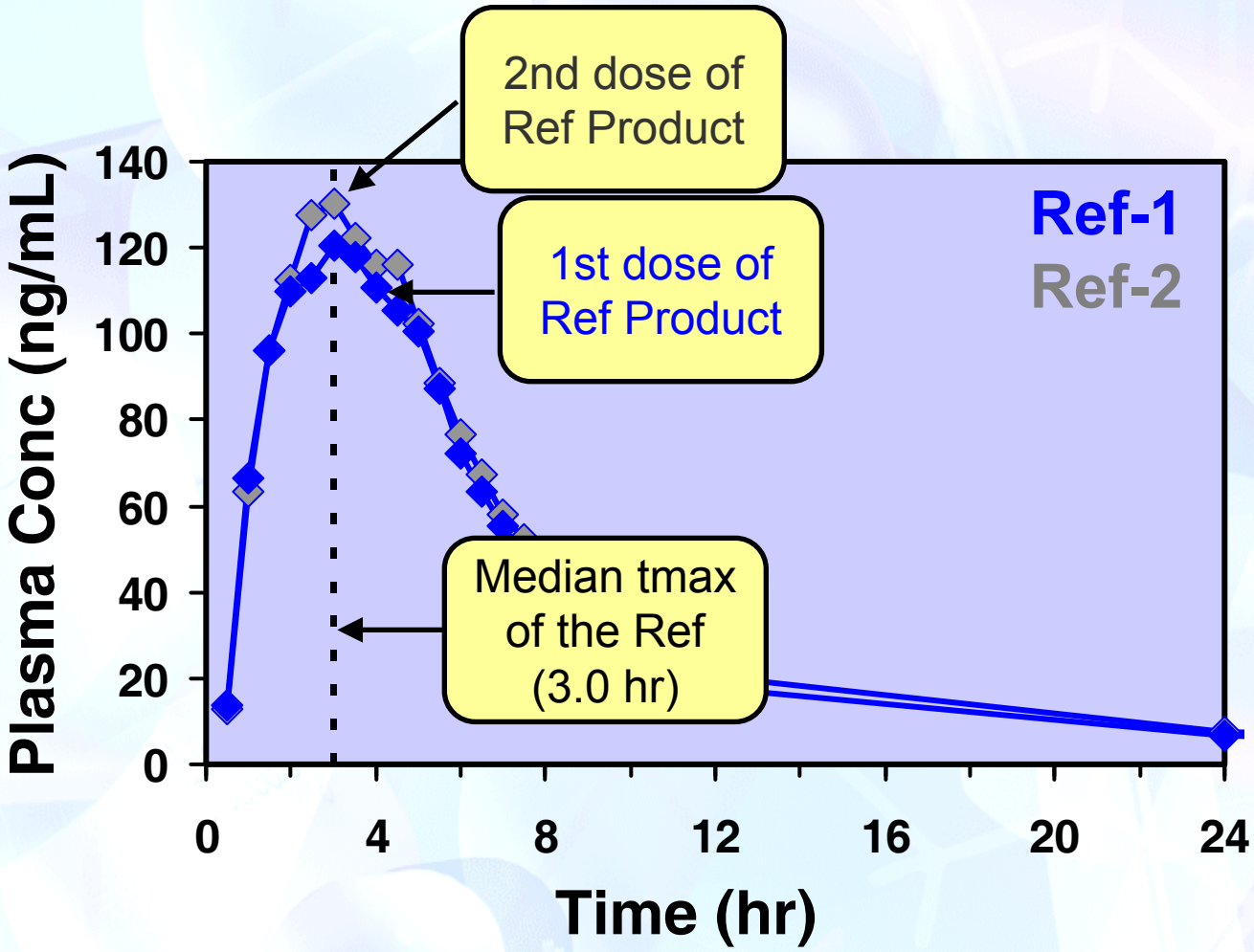
Bupropion SR Formulation, 150 mg



Bupropion SR Formulation, 150 mg
Test vs. Test

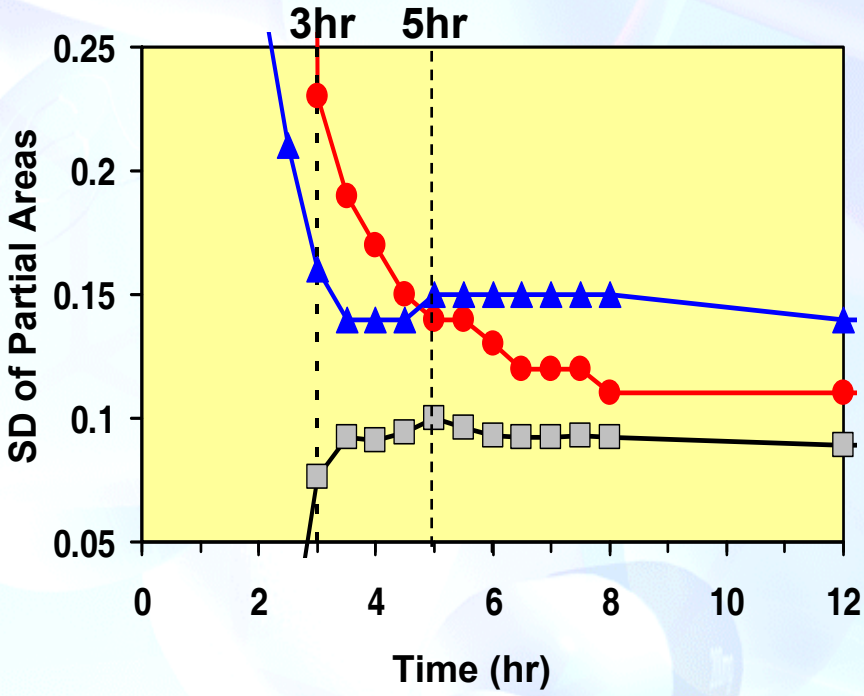


Bupropion SR Formulation, 150 mg
Reference vs. Reference



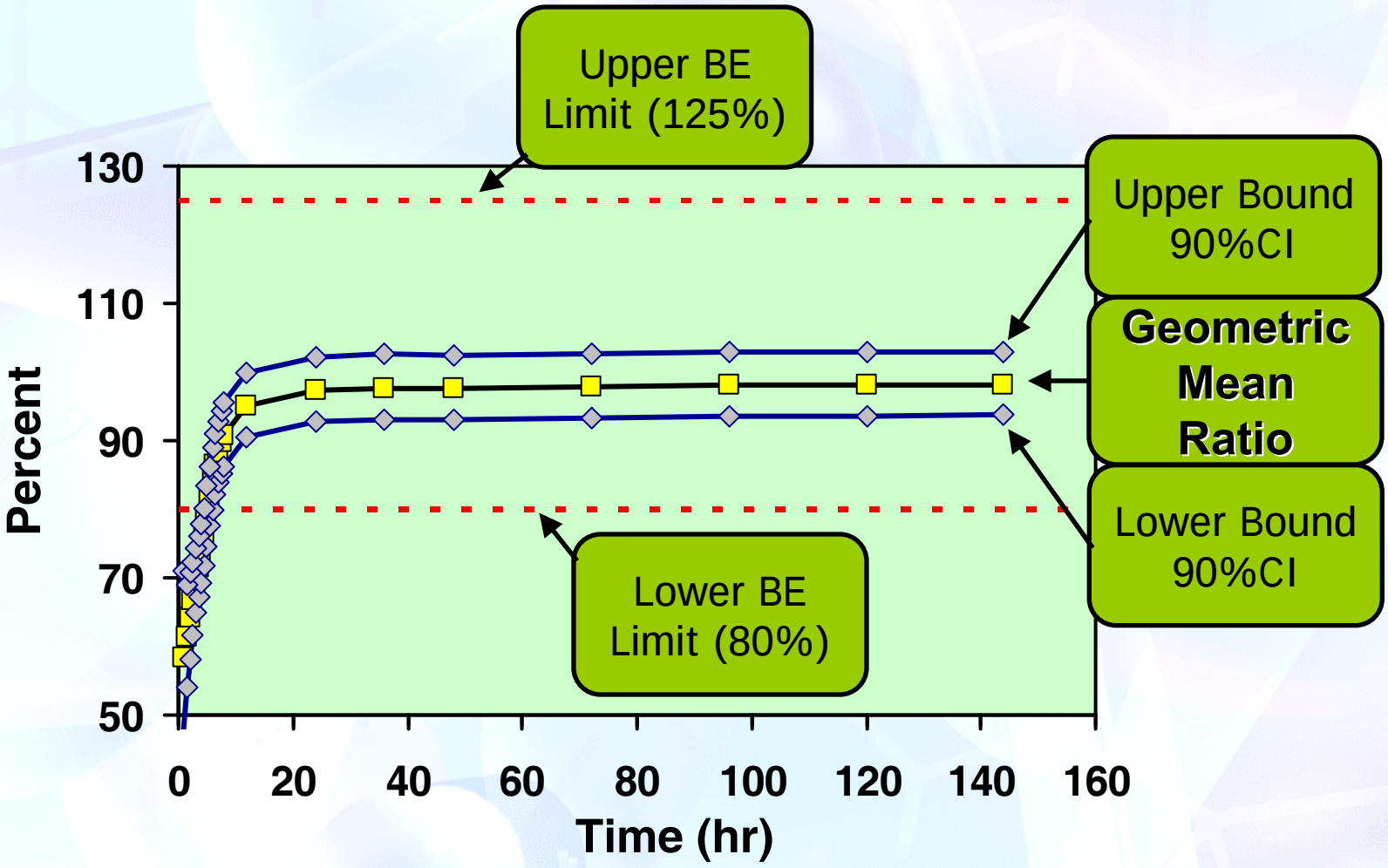
Bupropion SR Formulation, 150 mg
SDs of the Partial Areas

- The Test Product was more highly variable at early time points

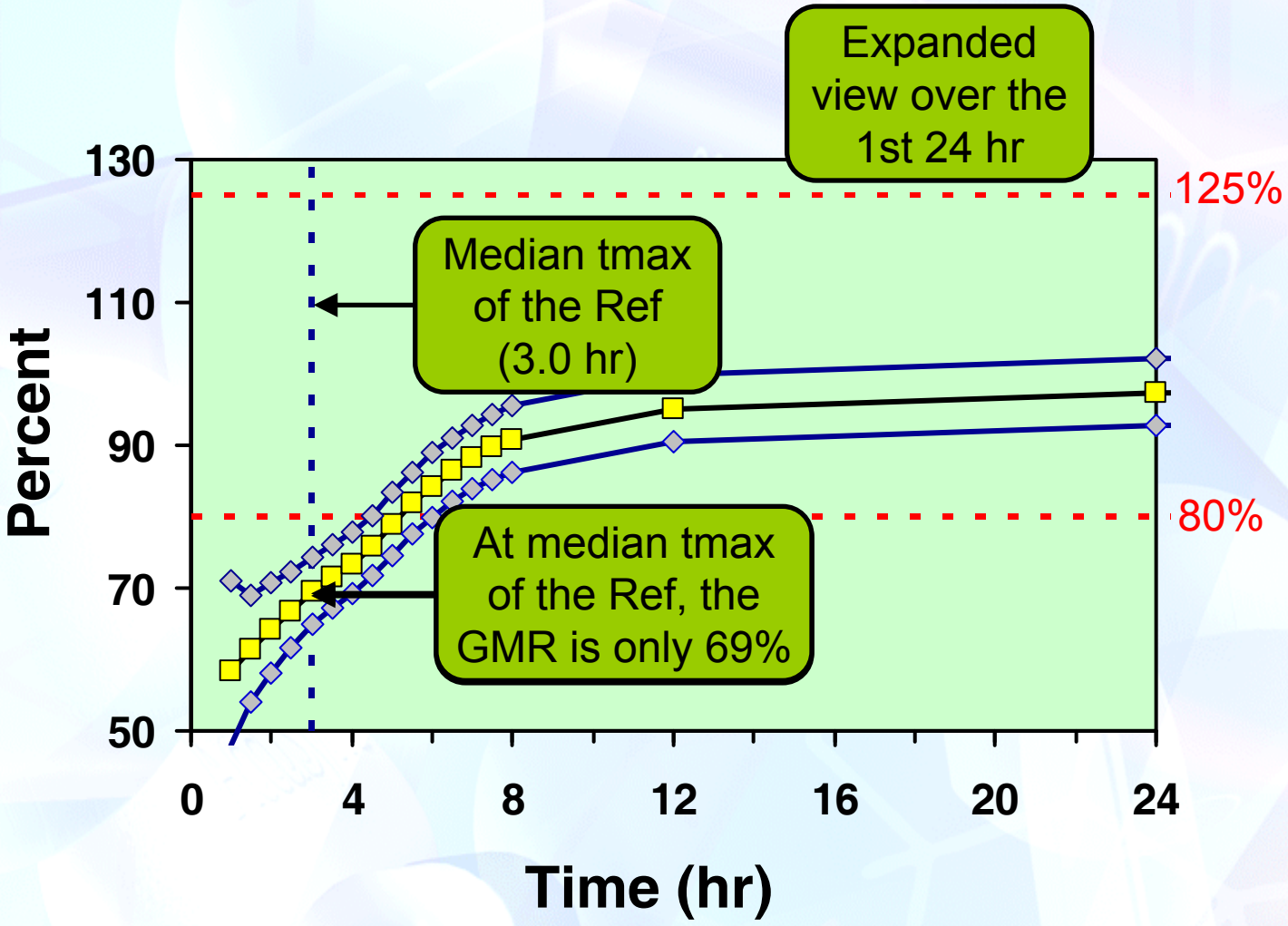


- At 5 hours and beyond, the Reference product had the higher variability
- At Median tmax (3.0 hr) the SDs were as follows
  - Swr: 0.16
  - Swt: 0.26
  - Sd: 0.08

Bupropion SR (Fasting) GMRs 90%CIs of the Partial Areas



Bupropion SR (Fasting) GMRs
90%CIs of the Partial Areas (Expanded)



Bupropion SR 150 mg (Fasting)
BE Analysis

	AUCp	Cmax	AUClast
GMR%	69	88	98
90%CI	64-75	82-94	93-103
CV%	21.6	19.6	15.0
ABE4	Fail	Pass	Pass

ANOVA: (MIXED) CV% calculated from estimates of Swr, Swt & Sd

Bupropion SR Fasting Study Conclusions

- No evidence of 'dose dumping' after administration of the Test formulation
- Early Exposure
  - AUCp failed because the GMR was low (<80%)
- Peak exposure and total exposure fell within the BE limits of 80-125%
- Bupropion SR study provides an example where AUCp is not important for clinical efficacy and onset and WSV values are low (not highly variable)

WSV Associated with AUCp During Absorption

- From our experience WSV is generally greater during the absorptive phases of most oral drug products and therefore the BE limits on AUCp should take this into consideration

- Other examples to illustrate WSV and BE limits include, an analgesic, an angiotensin II receptor blocker and a lipid lowering agent

An Analgesic (for chronic pain)

ANALGESIC

CONFIDENCE INTERVALS
Partial AUC - Ln Scale
52 Subjects

Test vs Reference 1

Time	Test Mean	Ref 1 Mean	%Geometric Mean Ratio	Lower C.I.	Upper C.I.	C.V.%
0.5 hr	0.23129	0.47662	78.2448	54.857	111.605	94.03
1 hr	1.99377	2.35974	69.3527	51.974	92.542	80.51
1.5 hr	3.16171	3.45303	74.7277	59.219	94.298	64.93
2 hr	3.92497	4.15123	79.7510	65.832	96.613	53.54
3 hr	4.87930	5.01119	87.6442	76.881	99.914	36.57
4 hr	5.46498	5.55512	91.3803	82.870	100.765	27.29
5 hr	5.88105	5.95178	93.1713	86.520	100.334	20.67
6 hr	6.19876	6.25705	94.3373	88.723	100.306	17.13
7 hr	6.44729	6.50145	94.7276	89.523	100.235	15.77
8 hr	6.65308	6.70710	94.7405	89.856	99.890	14.77
9 hr	6.83109	6.88242	94.9963	90.484	99.733	13.58
10 hr	6.98493	7.03108	95.4902	91.339	99.830	12.41
11 hr	7.11591	7.15923	95.7607	91.916	99.767	11.44
12 hr	7.22459	7.26680	95.8667	92.278	99.595	10.65
13 hr	7.31332	7.35505	95.9129	92.541	99.407	9.99
14 hr	7.38840	7.43030	95.8966	92.687	99.217	9.50
16 hr	7.50617	7.54852	95.8540	92.804	99.004	9.02
18 hr	7.59206	7.63573	95.7265	92.715	98.836	8.92
20 hr	7.65588	7.70093	95.5949	92.584	98.704	8.93
24 hr	7.74020	7.78742	95.3878	92.308	98.571	9.16
36 hr	7.83469	7.88949	94.6674	91.354	98.101	9.95
48 hr	7.86235	7.91657	94.7221	91.324	98.247	10.20

An Analgesic (for chronic pain)

ANALGESIC

CONFIDENCE INTERVALS
Partial AUC - Ln Scale
52 Subjects

Test vs Reference 2

Time	Test Mean	Ref 2 Mean	%Geometric Mean Ratio	Lower C.I.	Upper C.I.	C.V.%
0.5 hr	0.23129	0.24397	98.741	69.018	141.264	94.03
1 hr	1.99377	1.99487	99.890	74.452	134.021	80.51
1.5 hr	3.16171	3.12829	103.398	81.579	131.053	64.93
2 hr	3.92497	3.89045	103.512	85.136	125.855	53.54
3 hr	4.87930	4.89641	98.304	86.018	112.344	36.57
4 hr	5.46498	5.51138	95.466	86.415	105.465	27.29
5 hr	5.88105	5.93738	94.523	87.652	101.932	20.67
6 hr	6.19876	6.25992	94.067	88.366	100.135	17.13
7 hr	6.44729	6.51686	93.279	88.059	98.808	15.77
8 hr	6.65308	6.72853	92.732	87.863	97.871	14.77
9 hr	6.83109	6.90600	92.782	88.294	97.499	13.58
10 hr	6.98493	7.05513	93.221	89.093	97.540	12.41
11 hr	7.11591	7.17988	93.803	89.967	97.803	11.44
12 hr	7.22459	7.28199	94.422	90.822	98.164	10.65
13 hr	7.31332	7.36523	94.941	91.542	98.467	9.99
14 hr	7.38840	7.43614	95.338	92.088	98.703	9.50
16 hr	7.50617	7.54678	96.020	92.908	99.236	9.02
18 hr	7.59206	7.62750	96.518	93.425	99.713	8.92
20 hr	7.65588	7.68778	96.860	93.752	100.071	8.93
24 hr	7.74020	7.76807	97.252	94.053	100.559	9.16
36 hr	7.83469	7.85725	97.769	94.283	101.383	9.95
48 hr	7.86235	7.88374	97.884	94.307	101.597	10.20

An Analgesic (for chronic pain)

ANALGESIC

CONFIDENCE INTERVALS
Partial AUC - Ln Scale
52 Subjects

Reference 1 vs Reference 2
Median Tmax for Test = 9 hr
Median Tmax for Ref = 9 hr

Time	Ref 1 Mean	Ref 2 Mean	%Geometric Mean Ratio	Lower C.I.	Upper C.I.	C.V.%
0.5 hr	0.47662	0.24397	126.194	81.634	195.079	94.03
1 hr	2.35974	1.99487	144.033	100.764	205.882	80.51
1.5 hr	3.45303	3.12829	138.366	103.732	184.564	64.93
2 hr	4.15123	3.89045	129.794	102.350	164.598	53.54
3 hr	5.01119	4.89641	112.162	95.362	131.923	36.57
4 hr	5.55512	5.51138	104.471	92.558	117.918	27.29
5 hr	5.95178	5.93738	101.451	92.559	111.196	20.67
6 hr	6.25705	6.25992	99.713	92.417	107.586	17.13
7 hr	6.50145	6.51686	98.471	91.814	105.610	15.77
8 hr	6.70710	6.72853	97.880	91.669	104.511	14.77
9 hr	6.88242	6.90600	97.670	91.957	103.737	13.58
10 hr	7.03108	7.05513	97.624	92.395	103.149	12.41
11 hr	7.15923	7.17988	97.956	93.108	103.056	11.44
12 hr	7.26680	7.28199	98.493	93.947	103.258	10.65
13 hr	7.35505	7.36523	98.987	94.696	103.473	9.99
14 hr	7.43030	7.43614	99.418	95.313	103.698	9.50
16 hr	7.54852	7.54678	100.173	96.241	104.266	9.02
18 hr	7.63573	7.62750	100.827	96.913	104.898	8.92
20 hr	7.70093	7.68778	101.324	97.386	105.421	8.93
24 hr	7.78742	7.76807	101.954	97.892	106.184	9.16
36 hr	7.88949	7.85725	103.276	98.817	107.935	9.95
48 hr	7.91657	7.88374	103.338	98.767	108.122	10.20

An Angiotensin II Receptor Blocker

ANGIOTENSIN II-RECEPTOR BLOCKER

CONFIDENCE INTERVALS
Partial AUC - Ln Scale
63 Subjects

Test vs Reference 1

Time	Test Mean	Ref 1 Mean	%Geometric Mean Ratio	Lower C.I.	Upper C.I.	C.V.%
0.5 hr	5.6890	5.4872	122.360	95.606	156.601	75.65
1 hr	7.3407	7.1791	117.543	96.535	143.124	60.37
1.5 hr	8.2144	8.1038	111.698	95.111	131.177	49.29
2 hr	8.7600	8.6707	109.335	95.100	125.701	42.77
2.33 hr	9.0356	8.9479	109.168	96.041	124.088	39.28
2.67 hr	9.2712	9.1958	107.834	95.834	121.337	36.17
3 hr	9.4637	9.3913	107.508	96.399	119.898	33.44
3.33 hr	9.6280	9.5631	106.698	96.411	118.083	31.08
3.67 hr	9.7720	9.7140	105.969	96.391	116.498	29.04
4 hr	9.8929	9.8414	105.291	96.289	115.135	27.40
4.5 hr	10.0527	10.0107	104.289	95.997	113.298	25.40
5 hr	10.1778	10.1435	103.488	95.643	111.976	24.17
5.5 hr	10.2658	10.2365	102.973	95.380	111.170	23.48
6 hr	10.3302	10.3042	102.632	95.201	110.643	23.04
7 hr	10.4225	10.4000	102.270	95.031	110.061	22.51
8 hr	10.4880	10.4670	102.125	95.003	109.781	22.16
9 hr	10.5398	10.5198	102.021	94.996	109.565	21.87
10 hr	10.5835	10.5645	101.922	94.993	109.357	21.59
12 hr	10.6494	10.6319	101.765	94.972	109.043	21.18
16 hr	10.7196	10.7046	101.515	94.846	108.654	20.84
24 hr	10.7822	10.7711	101.125	94.590	108.111	20.48
36 hr	10.8259	10.8151	101.087	94.684	107.924	20.07
48 hr	10.8470	10.8354	101.167	94.836	107.920	19.81

An Angiotensin II Receptor Blocker

ANGIOTENSIN II-RECEPTOR BLOCKER

CONFIDENCE INTERVALS
Partial AUC - Ln Scale
63 Subjects

Test vs Reference 2

Time	Test Mean	Ref 2 Mean	%Geometric Mean Ratio	Lower C.I.	Upper C.I.	C.V.%
0.5 hr	5.6890	5.5161	118.884	92.890	152.152	75.65
1 hr	7.3407	7.1298	123.487	101.416	150.361	60.37
1.5 hr	8.2144	7.9950	124.528	106.036	146.245	49.29
2 hr	8.7600	8.5446	124.033	107.884	142.599	42.77
2.33 hr	9.0356	8.8266	123.243	108.425	140.087	39.28
2.67 hr	9.2712	9.0676	122.576	108.935	137.925	36.17
3 hr	9.4637	9.2675	121.675	109.102	135.697	33.44
3.33 hr	9.6280	9.4400	120.684	109.049	133.561	31.08
3.67 hr	9.7720	9.5912	119.812	108.983	131.717	29.04
4 hr	9.8929	9.7186	119.047	108.868	130.177	27.40
4.5 hr	10.0527	9.8861	118.133	108.740	128.337	25.40
5 hr	10.1778	10.0178	117.344	108.449	126.968	24.17
5.5 hr	10.2658	10.1119	116.635	108.035	125.920	23.48
6 hr	10.3302	10.1810	116.088	107.683	125.149	23.04
7 hr	10.4225	10.2805	115.256	107.098	124.036	22.51
8 hr	10.4880	10.3521	114.557	106.568	123.145	22.16
9 hr	10.5398	10.4093	113.937	106.092	122.363	21.87
10 hr	10.5835	10.4582	113.354	105.648	121.622	21.59
12 hr	10.6494	10.5319	112.462	104.956	120.506	21.18
16 hr	10.7196	10.6098	111.604	104.272	119.452	20.84
24 hr	10.7822	10.6790	110.877	103.712	118.538	20.48
36 hr	10.8259	10.7273	110.365	103.373	117.829	20.07
48 hr	10.8470	10.7526	109.898	103.021	117.234	19.81

An Angiotensin II Receptor Blocker

ANGIOTENSIN II-RECEPTOR BLOCKER

CONFIDENCE INTERVALS
Partial AUC - Ln Scale
63 Subjects

Reference 1 vs Reference 2
Median Tmax of Test = 3 hr
Median Tmax of Ref = 3.33 hr

Time	Ref 1 Mean	Ref 2 Mean	%Geometric Mean Ratio	Lower C.I.	Upper C.I.	C.V.%
0.5 hr	5.4872	5.5161	97.159	71.569	131.898	75.65
1 hr	7.1791	7.1298	105.056	82.315	134.080	60.37
1.5 hr	8.1038	7.9950	111.486	91.354	136.054	49.29
2 hr	8.6707	8.5446	113.443	95.439	134.843	42.77
2.33 hr	8.9479	8.8266	112.894	96.326	132.311	39.28
2.67 hr	9.1958	9.0676	113.672	98.214	131.562	36.17
3 hr	9.3913	9.2675	113.177	98.872	129.552	33.44
3.33 hr	9.5631	9.4400	113.108	99.758	128.246	31.08
3.67 hr	9.7140	9.5912	113.063	100.543	127.143	29.04
4 hr	9.8414	9.7186	113.064	101.213	126.303	27.40
4.5 hr	10.0107	9.8861	113.274	102.224	125.519	25.40
5 hr	10.1435	10.0178	113.389	102.838	125.021	24.17
5.5 hr	10.2365	10.1119	113.268	103.014	124.543	23.48
6 hr	10.3042	10.1810	113.110	103.054	124.149	23.04
7 hr	10.4000	10.2805	112.697	102.899	123.429	22.51
8 hr	10.4670	10.3521	112.173	102.564	122.683	22.16
9 hr	10.5198	10.4093	111.680	102.233	122.001	21.87
10 hr	10.5645	10.4582	111.216	101.926	121.353	21.59
12 hr	10.6319	10.5319	110.512	101.448	120.387	21.18
16 hr	10.7046	10.6098	109.938	101.061	119.595	20.84
24 hr	10.7711	10.6790	109.644	100.934	119.105	20.48
36 hr	10.8151	10.7273	109.178	100.675	118.398	20.07
48 hr	10.8354	10.7526	108.631	100.273	117.685	19.81

A Lipid Lowering Agent

LIPID LOWERING AGENT

CONFIDENCE INTERVALS
Partial AUC - Ln Scale
43 Subjects

Test vs Reference 1

Time	Test Mean	Ref 1 Mean	%Geometric Mean Ratio	Lower C.I.	Upper C.I.	C.V.%
0.5 hr	-0.31204	-0.25550	94.503	64.977	137.445	94.82
1 hr	1.64316	1.59300	105.144	81.425	135.772	65.08
1.5 hr	2.56823	2.52603	104.310	83.888	129.705	55.47
2 hr	3.08387	3.03197	105.326	87.892	126.219	46.07
2.5 hr	3.39164	3.34094	105.200	89.807	123.232	40.27
3 hr	3.61084	3.53937	107.409	93.338	123.602	35.75
3.5 hr	3.76230	3.68472	108.067	95.013	122.915	32.77
4 hr	3.87217	3.78825	108.754	96.357	122.746	30.81
5 hr	4.02315	3.94665	107.951	96.893	120.270	27.51
6 hr	4.12013	4.04592	107.703	97.372	119.131	25.67
7 hr	4.18526	4.11513	107.265	97.436	118.084	24.46
8 hr	4.23261	4.16812	106.661	97.205	117.038	23.63
10 hr	4.30433	4.25185	105.388	96.517	115.074	22.38
12 hr	4.35092	4.31097	104.076	95.596	113.309	21.64
15 hr	4.38834	4.35707	103.177	94.867	112.216	21.38
24 hr	4.44177	4.41654	102.555	94.281	111.555	21.41

A Lipid Lowering Agent

LIPID LOWERING AGENT

CONFIDENCE INTERVALS
Partial AUC - Ln Scale
43 Subjects

Test vs Reference 2

Time	Test Mean	Ref 2 Mean	%Geometric Mean Ratio	Lower C.I.	Upper C.I.	C.V.%
0.5 hr	-0.31204	0.00192	73.0547	50.018	106.700	94.82
1 hr	1.64316	1.78826	86.4943	66.701	112.161	65.08
1.5 hr	2.56823	2.65884	91.3378	73.192	113.982	55.47
2 hr	3.08387	3.13964	94.5754	78.686	113.674	46.07
2.5 hr	3.39164	3.43699	95.5663	81.371	112.238	40.27
3 hr	3.61084	3.63885	97.2376	84.304	112.156	35.75
3.5 hr	3.76230	3.78445	97.8092	85.812	111.483	32.77
4 hr	3.87217	3.89577	97.6673	86.362	110.453	30.81
5 hr	4.02315	4.04124	98.2081	87.992	109.610	27.51
6 hr	4.12013	4.13487	98.5366	88.937	109.172	25.67
7 hr	4.18526	4.20002	98.5348	89.365	108.645	24.46
8 hr	4.23261	4.24975	98.3000	89.448	108.028	23.63
10 hr	4.30433	4.32442	98.0112	89.632	107.174	22.38
12 hr	4.35092	4.37002	98.1077	89.988	106.960	21.64
15 hr	4.38834	4.40729	98.1232	90.095	106.866	21.38
24 hr	4.44177	4.46503	97.7003	89.694	106.422	21.41

A Lipid Lowering Agent

LIPID LOWERING AGENT

CONFIDENCE INTERVALS
Partial AUC - Ln Scale
43 Subjects

Reference 1 vs Reference 2
Median Tmax of Test = 1.5 hr
Median Tmax of Ref = 1.5 hr

Time	Ref 1 Mean	Ref 2 Mean	%Geometric Mean Ratio	Lower C.I.	Upper C.I.	C.V.%
0.5 hr	-0.25550	0.00192	77.3042	48.958	122.062	94.82
1 hr	1.59300	1.78826	82.2629	60.164	112.478	65.08
1.5 hr	2.52603	2.65884	87.5634	67.069	114.320	55.47
2 hr	3.03197	3.13964	89.7928	71.957	112.050	46.07
2.5 hr	3.34094	3.43699	90.8422	74.853	110.246	40.27
3 hr	3.53937	3.63885	90.5300	76.237	107.503	35.75
3.5 hr	3.68472	3.78445	90.5078	77.316	105.951	32.77
4 hr	3.78825	3.89577	89.8057	77.443	104.142	30.81
5 hr	3.94665	4.04124	90.9749	79.706	103.837	27.51
6 hr	4.04592	4.13487	91.4891	80.868	103.505	25.67
7 hr	4.11513	4.20002	91.8615	81.670	103.325	24.46
8 hr	4.16812	4.24975	92.1607	82.264	103.248	23.63
10 hr	4.25185	4.32442	93.0007	83.514	103.565	22.38
12 hr	4.31097	4.37002	94.2655	84.954	104.598	21.64
15 hr	4.35707	4.40729	95.1015	85.814	105.394	21.38
24 hr	4.41654	4.46503	95.2661	85.947	105.595	21.41

WSV on AUCp Comment

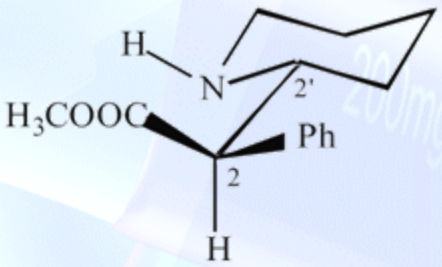
- The forgoing examples clearly show that WSV associated with AUCp during the absorptive phases are very large.
- This must be taken into consideration for setting BE limits.
- May require scaled ABE approaches which I will discuss later

Some Examples Where Rapid Onset is of Clinical Importance

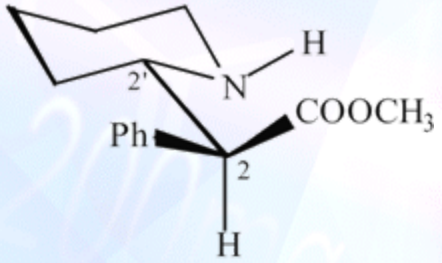
- Methylphenidate HCl Sustained Release/Extended Release Drug Products
- Zolpidem tartrate Extended Release Drug Product

Stereochemistry of MPH

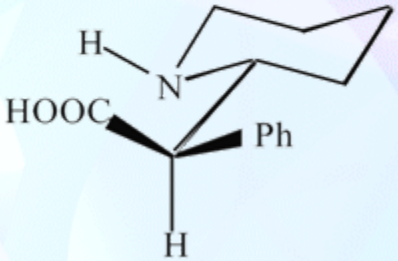
- MPH has two asymmetric carbon atoms
- There are four optical isomers
  - Two pairs of enantiomers
  - *threo* and *erythro*
- Commercial MPH is dl-*threo*-MPH



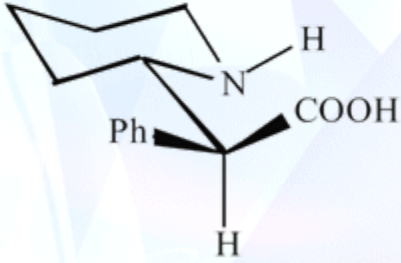
d (+) Methylphenidate 2R, 2'R



l (-) Methylphenidate 2S, 2'S



d (+) Ritalinic Acid (2R, 2'R)



l (-) Ritalinic Acid (2S, 2'S)

Methylphenidate MR Drug Product Major Attributes

- 3 Major considerations:
  - Rapid onset of action – rate of rise in plasma drug level post dose
  - Longer duration of effect
  - Absence of inducing tolerance

Approved Methylphenidate MR (SR/ER) Products

- Concerta (Oros)
- Metadate CD
- Metadate SR/ER
- Ritalin LA
- Ritalin SR
- Focalin XR

- All these formulations are clinically effective
- Evaluation of multi-source products of each of these brand MR products must provide therapeutic equivalence to assure switchability to their respective reference listed drug products (brand)

FDA-Approved Major Methylphenidate Solid Oral MR Drug Products

- Methyphenidate HCl MR Capsule
  - Ritalin LA, 10 mg, 20 mg, 30 mg, 40 mg – Novartis
  - Metadate CD, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg – UCB, Inc.
  - Focalin XR, 5 mg, 10 mg, 20 mg, 30 mg – Novartis
- Methyphenidate HCl MR Tablet
  - Methylin ER, 5 mg, 10 mg, 20 mg – Mallinckrodt
  - Ritalin SR, 20 mg – Novartis
  - Concerta, 18 mg, 27 mg, 36 mg, 54 mg – Ortho McNeil Janssen
  - Metadate ER, 10 mg, 20 mg – UCB Inc.

Methylphenidate MR Drug Products Formulation

- **Concerta Tablet**
  - IR (22%) – outer coat / ER (78%) – inner core (Oros release mechanism)
- **Metadate CD Capsule**
  - IR beads (30%)/ER beads (70%)
- **Metadate ER Tablet***
- **Ritalin LA Capsule**
  - IR beads (50%)/ER beads (50%)
- **Ritalin SR***
- **Focalin XR Capsule**
  - IR beads (50%)/ER beads (50%)
- **Generic Methylphenidate ER products***

Bioequivalent products

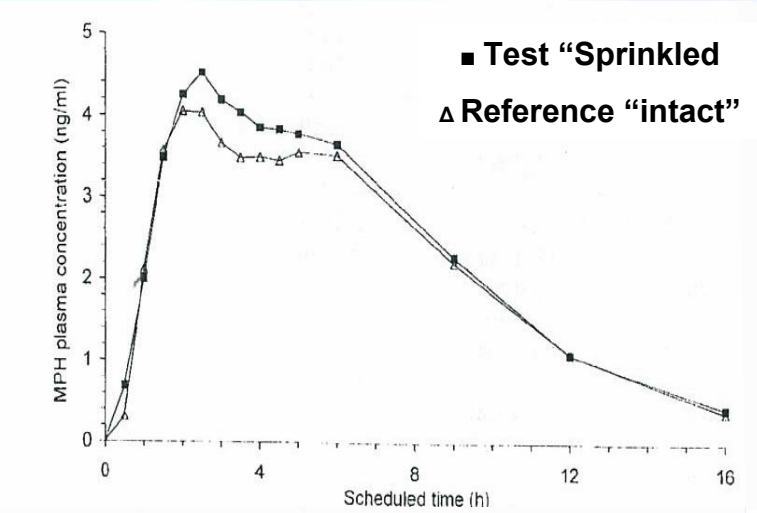
Wolraich ML et al, CNS Drugs, 2004, 18: 243.

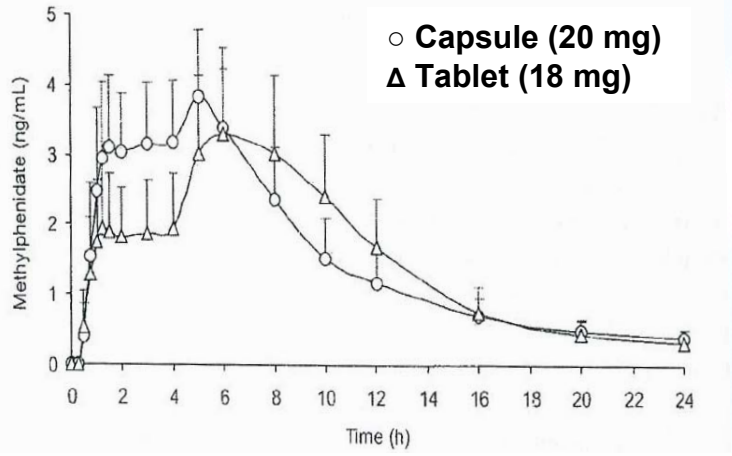
Diversity of Methylphenidate Drug Products

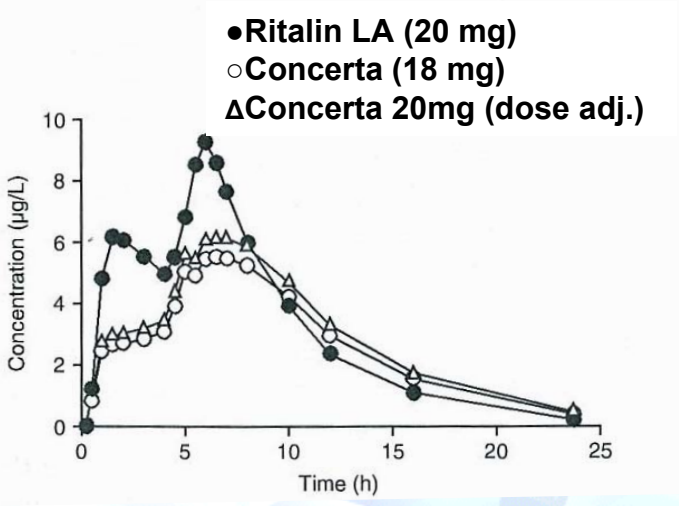
Drug Products	Age Range	Onset of Action	Peak Clinical Effect	Duration of Action	Number of Daily Doses
IR Products					
Ritalin, Metadate and others	6 yrs	30-60 min	ca. 2 hours (0.3-4 hrs)	2 - 4 hrs.	2 - 3
SR Products					
Ritalin SR, Metadate ER	6 yrs	60-90 min	ca. 5 hrs 1.3-8.2 hrs)	4 - 6 hrs	2
ER Products					
Metadate CD, Ritalin LA	6 – 15 yrs	30 min – 2 hrs	Bimodal pattern	6 – 8 hrs	1 - 2
Concerta	6 – 65 yrs	30 min – 2hrs	Ascending pattern	12 hrs	1

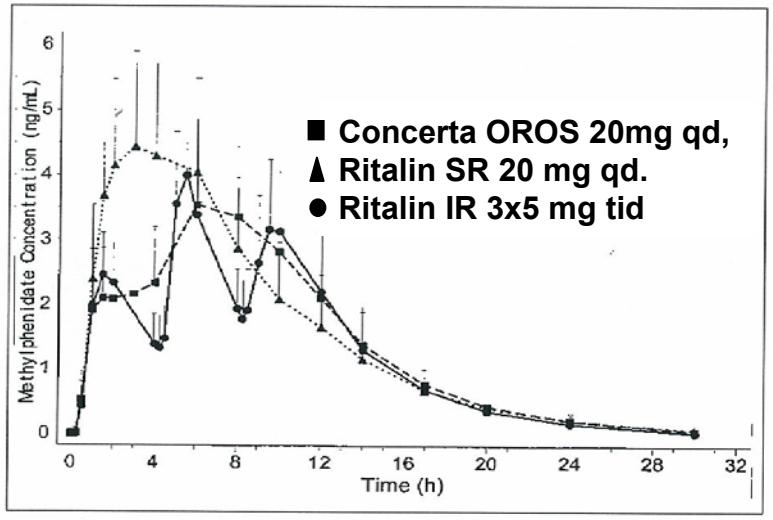
Biedman J, Medscape Psychiatry and Mental Health, 2003, 8

Diversity in the Drug Release Profiles of Various Methylphenidate ER Products









Presentation to USFDA 2010, Washington, DC

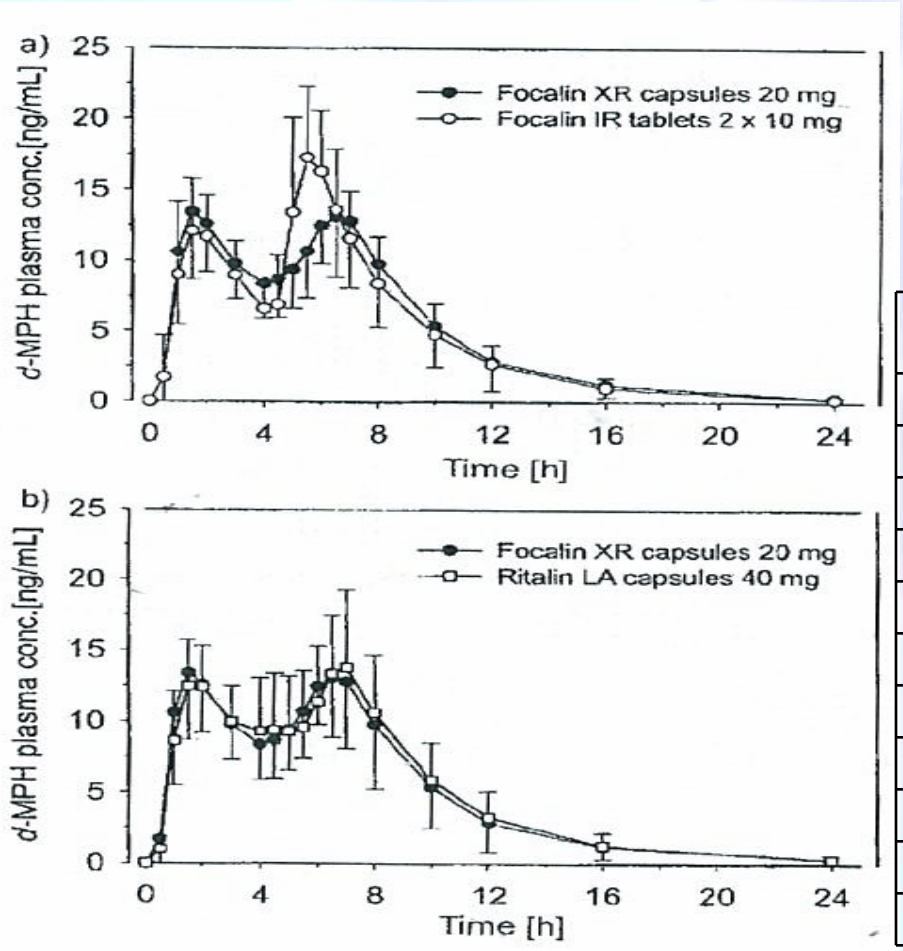
ADHD Activity of MPH

- Clinical efficacy in terms of ADHD only resides in the d-isomer of threo-MPH and the l-isomer is devoid of this activity*.
- The d-isomer is marketed as Focalin® available as immediate (IR) and extended release (XR) formulations.

* Srinivas et al Clin. Pharmcol. Therap. 52, 561, 1992

*Medians

d-*threo*-Methylphenidate Drug Products Pulsatile/Bimodal Pharmacokinetic Release



Mean dexmethylphenidate plasma concentrations-time profiles after administration of d-methylphenidate ER capsule 20 mg (Focalin XR), d-methylphenidate IR tablet 2x10 mg (Focalin), and d,l-methylphenidate ER capsule 40 mg (Ritalin LA)

Results: (N=25)

Parameter	ER d-MPH vs IR d-MPH		ER d-MPH vs d,l-MPH	
	PE	90%(CI)	PE	90%(CI)
AUC(0-t)	1.02	98-107%	0.97	94-100%
AUC(0-inf)	1.02	98-107%	0.97	94-100%
AUC(0-4)	1.11	105-117%	1.03	98-108%
AUC(4-10)	0.95	91-100%	0.97	94-100%
Cmax	0.86	81-91%	0.95	91-99%
Cmax 1 (0-4)	1.06	100-113%	1.01	96-106%
Cmax 2(4-10)	0.82	77-88%	0.92	87-96%
Tmax*	5.8h	5.5h	5.8h	6.5h
Tmax1(0-4)*	1.5h	1.5h	1.5h	2.0h
Tmax2(4-10)*	6.5h	5.5h	6.5h	6.5h

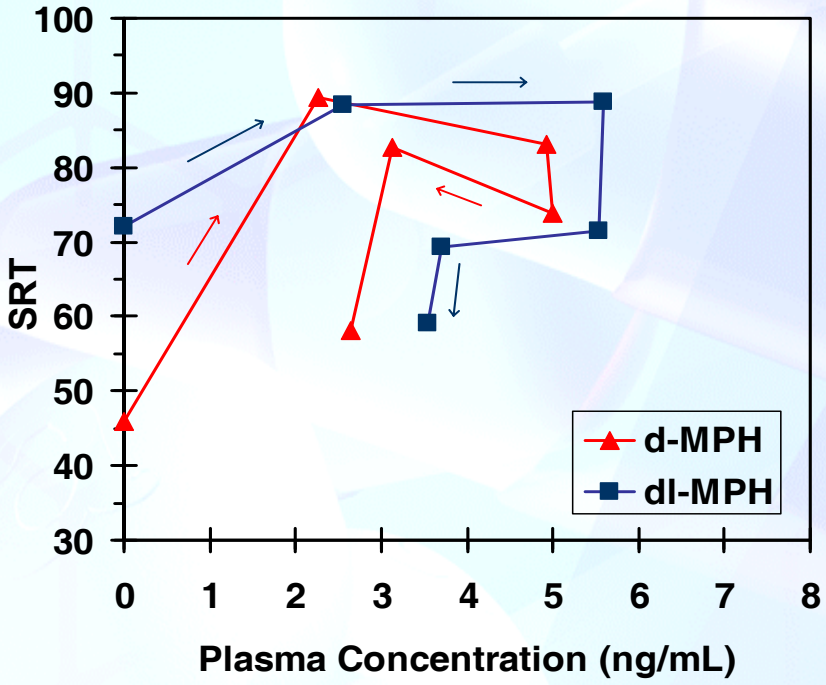
*Medians

Tuerck D et al, Int J Clin Pharmacol Therap, 45, 662-668, 2007

Diversity in the Drug Release and Plasma Profiles of various Methylphenidate MR Products

- Formulation and release mechanism in vivo
  - Unimodal
  - Bimodal (double peak)
  - Ascending pattern with plateau
- These profiles are observed from:
  - IR/ER combination formulation
- Dosing regimen and duration of efficacy varies among different formulations
  - Each product is efficacious in it's own right
  - Evaluation of early exposure from the plasma drug concentration profile (**AUCp**) is important for onset of action comparison

Methylphenidate (MPH) IR Drug Products PK-PD Relationship -Tolerance Issue



Positive hysteresis loop between Scanning Reaction Time (SRT) scores and plasma levels of d-MPH

(Srinivas NR et al, Clinical Pharmacol Therap 1992)

PK/PD Study in ADHD in Children (N=6)

d, l, dl-MPH and placebo

- 4-way double blind cross-over design
- d,l-MPH (10 mg), d-MPH (5 mg), l-MPH (5 mg), and placebo randomized
- each phase administered one week apart

PD Studies:

-The computer tests each took 5 minutes run one after the other VSM, then TSA, then SRT a total of 15 min

- SRT discriminated active drug from placebo
  - SRT is a continuous performance task
  - VSM and TSA were run prior to SRT to prolong the total period of concentration required

PD Endpoints:

-**VSM :** Visio Special Memory

-**TSA:** Trail Sequence A

-**SRT:** Scanning Reaction Time

Methylphenidate ER Drug Products Background

- Duration of Action
  - Rapid systemic uptake results in changed behavior within 1 hour of dosing IR or ER products
  - IR: 2-3 times/day, due to short duration of effect
  - The new MR products such as Ritalin LA, Focalin XR, Metadate CD and Concerta overcame the issue of frequency of dosing of IR MPH

Second Example

Zolpidem Tartrate ER (Ambien CR)

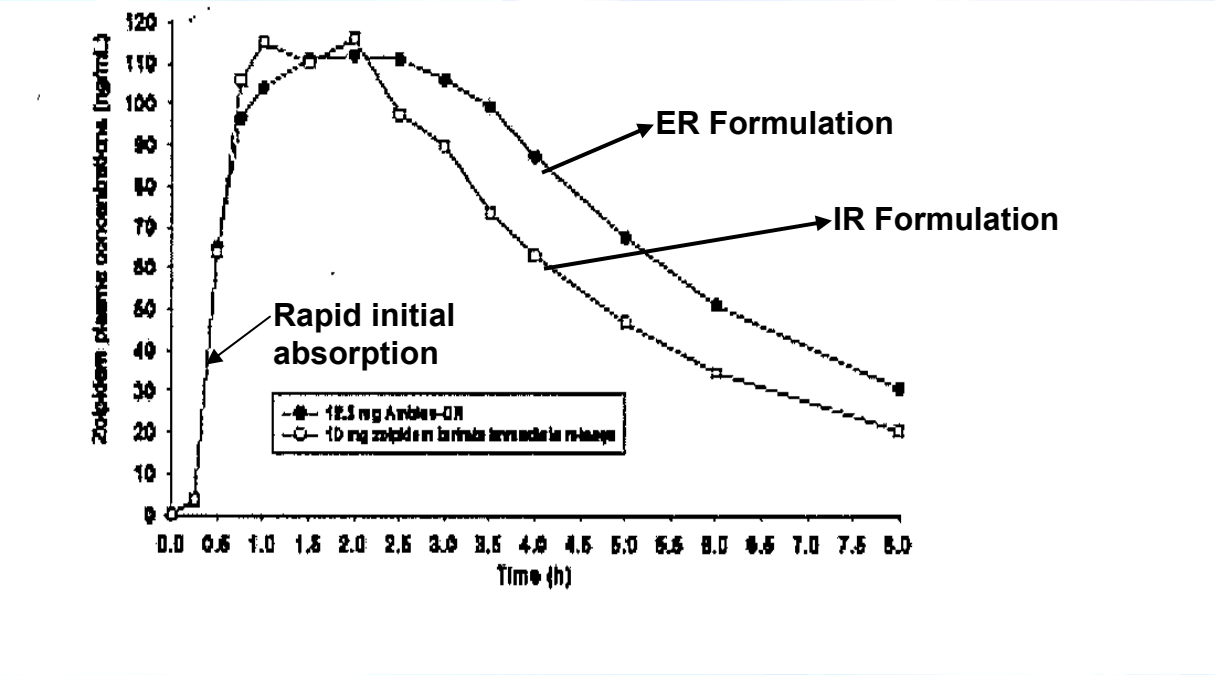
Zolpidem Tartrate Extended Release Drug Product (Ambien CR)

- Non-benzodiazepine sedative hypnotic
- Indication:
  - Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance
- Formulation:
  - Two-layer bi-phasic release tablet where ca. 60% of the dose is IR (delivered within 30 minutes) and the remainder of the tablet is extended release
- Dosage and Administration: Once a day
  - 12.5 mg immediately before bedtime (adults)
  - 6.25 mg immediately before bedtime (elderly patients)
  - 6.25 mg immediately before bedtime (hepatic impairment)

Zolpidem Tartrate Extended Release Drug Product (Ambien CR)

- Pharmacokinetics
  - Bi-phasic drug release,
  - Rapid initial absorption (onset), then extended plasma concentrations last beyond 3 hours after administration (sleep maintenance), rapid elimination (overcome residual effects)
  - Tmax: within 1.5-2 hr (0.9 hr IR formulation)
  - 92.5% protein-bound
  - Hepatically metabolized by CYP3A4
  - Elimination half-life: 2.8 hours, excreted as metabolites primarily in urine

Plasma Drug Concentrations – Time Profiles Zolpidem Tartrate ER Product (Ambien CR) and IR



Mean plasma concentration-time profiles for zolpidem ER tablet (Ambien CR) 12.5 mg tablet and IR zolpidem titrate tablet 10 mg

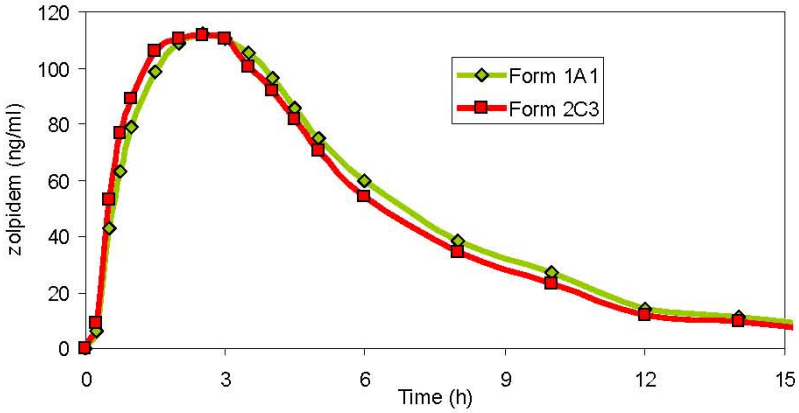
Ambien CR Labeling

Some Observations for Various MR Drug Products – Points to Consider

- Partial AUCs during the early period post-dosing consistently exhibit significantly high within-subject variability, thus making it difficult to statistically demonstrate BE (acceptable BE limits based on 90% CI) in a reasonable size study. This may require a scaling approach to establish acceptable BE limits.
- The point estimates during this early period of drug absorption post-dose may be unpredictable
- Therapeutic concentration range may not have been established for some of the drugs.
- Tmax and Cmax, being single points may not be accurately captured even by the study design because of the complexity of the formulation design.

Bioequivalence criteria for Zolpidem ER (Ambien CR®)

- Bioequivalence study marketed form vs development form
- N = 72 adults, two-way cross-over design
- Bioequivalence on all parameters, except $AUC_{0\text{-}1.5h}$
  - Point estimate within boundaries
  - 90%CI very wide (45% vs <20% others)
  - Very large intra-individual variability
  - Represents less than 10% of total AUC



	C_{max}	AUC_{inf}	$AUC_{0\text{-}1.5}$	$AUC_{1.5\text{-}inf}$	$AUC_{0\text{-}3}$	$AUC_{3\text{-}6}$	$AUC_{6\text{-}inf}$
Ln Ratio [90%CI]	1.02 [0.96 - 1.10]	0.99 [0.92 - 1.06]	1.22 [1.01 - 1.46]	0.96 [0.89 - 1.04]	1.08 [0.99 - 1.19]	0.97 [0.90 - 1.05]	0.94 [0.83 - 1.06]
Total CV%	46	61	62	65	47	60	95
Within- subject CV%	25	25	65	27	34	29	43

sanofi aventis
Because health matters

Partial AUCs as per FDA guidance

Zolpidem ER Fasting study in 37 subjects comparing Test and Reference formulations

	Test	Reference	90% Confidence Interval
$AUC_{0\text{-}1.5}$	124.85	133.82	(84.52, 102.98)
$AUC_{1.5\text{-}t}$	507.98	449.09	(104.28, 122.7)

A Proposal to the Agency for the Evaluation of MR Products: Application of AUCp

- **Identify MR drug products where AUCp is clinically important**
- **Published literature and FDA filed data be examined**
- **Perform simulations and actual studies to establish performance of the AUCp metric if necessary**
- **In order to apply AUCp as a BE metric, the reproducibility of the plasma profiles of two lots of the reference and test product should be examined**
  - Estimate the WSV of AUCp within lot and between lots of the reference product. When appropriate Scaled Average Bioequivalence (sABE) be applied
  - WSV of test lots should not be significantly different from the reference lots

Summary Comments

- With the development of innovative extended release formulations the current regulatory recommendations for BE documentation may not be sufficient for assuring comparable therapeutic effect for all modified release/controlled release multi-source (generic drug products.
- Different/additional appropriate BE metrics may be considered for formulations with different release mechanisms geared towards documented therapeutic effect
- Product/formulation specific BE recommendations may be necessary to demonstrate BE for some ER drug products.
  - For example AUCp may be appropriate on a case by case basis. However, it may not be applicable in all situations
- Any recommendation must be supported by scientific rational, experimental evidence, feasibility to demonstrate BE by the currently established experimental designs and approaches without significantly increasing producers risk.

Acknowledgements

- The authors gratefully acknowledge helpful discussions with the following:
  - Dr. Paul Fackler and Mr. Charlie DiLiberti, TEVA Pharmceutical Inc.
  - Mr. Jim Caro, Sanofi-Aventis.
  - Ms Maureen Rawson, Biostatistics Consultant
  - Dr. John Hubbard, University of Saskatchewan

PK Profile Comparison for Modified Release Products

Robert A. Lionberger, Ph.D.

Chemist, Office of Generic Drugs (OGD), OPS, CDER, FDA

Do We Need Profile Similarity?

- Equivalent AUC and C_{max} does not necessarily ensure that PK profiles are similar for MR products
- Do differences in the rate or time-course of drug exposure affect
  - Clinical safety and efficacy?
  - Product interchangeability?

One FDA Medical Officer's View

- Absent adequate PK/PD relationship data, we do not know how the shape of the concentration-time curve contributes to effectiveness
- In almost all cases, we have required a controlled clinical trial to establish effectiveness [of new MR formulation]
- We always offer sponsors the opportunity to provide adequate evidence that the shape of the curve has no effect on effectiveness
  - No sponsor has provided an adequate response to this request in our view

Another FDA Medical Officer's View

- If a drug has generally delayed therapeutic and adverse responses, small differences in the rate of release/absorption cannot lead to different clinical responses.
- If a drug is used at doses high on the dose response curve (for both effectiveness and tolerability) small differences in the rate of release cannot lead to different clinical response.

Office of Generic Drugs Interest in Profile Comparison

- MR Generic products do differ from the RLD in
  - Inactive ingredients
  - Manufacturing process
  - Release mechanism
  - In vitro dissolution (different pH dependence)
- Profile similarity may help ensure these differences are not significant
- When using QbD, we expect ANDA sponsors to target the RLD release profile

Core Questions

- Is there clinical or PD information that can define relevant time intervals for partial areas?
  - Examples in Barbara Davit's presentation
- What measure to use to evaluate PK profile similarity?
- How should PK profile similarity be used in evaluation of all MR generic products?

Profile Comparisons

- T_{max} Comparisons (Current Process)
  - Test and RLD T_{max} values are compared qualitatively; differences are evaluated clinically (by consult to OGD clinical team and then to OND review division)
  - Problem: No threshold for reviewer to decide when to consult

Define pAUC

- pAUC: partial AUC is the area under the plasma concentration profile calculated between two specified time points.
- AUCpR: pAUC(0-T_{max}[reference product]) or the partial AUC to the reference product T_{max}.
- The partial AUC concept may also be applied to time intervals that are not related to early exposure.
  - For example, a partial AUC_{8-16} could be proposed if there were a need to ensure equivalent drug exposure over that time interval.

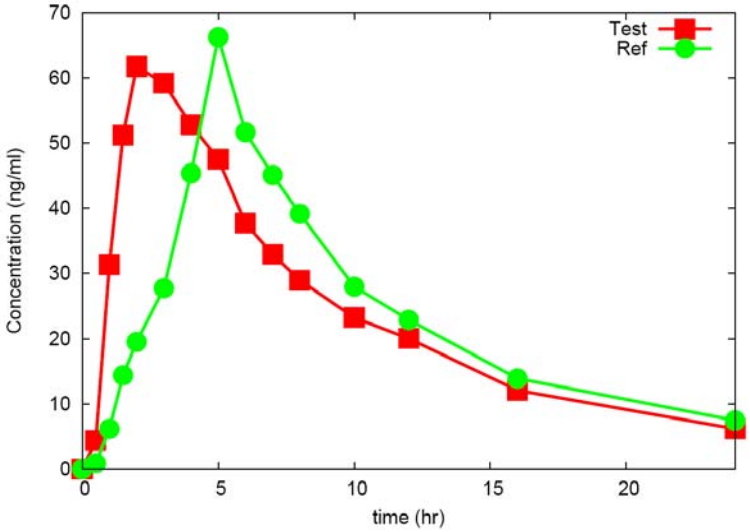
Is There a Best General pAUC?

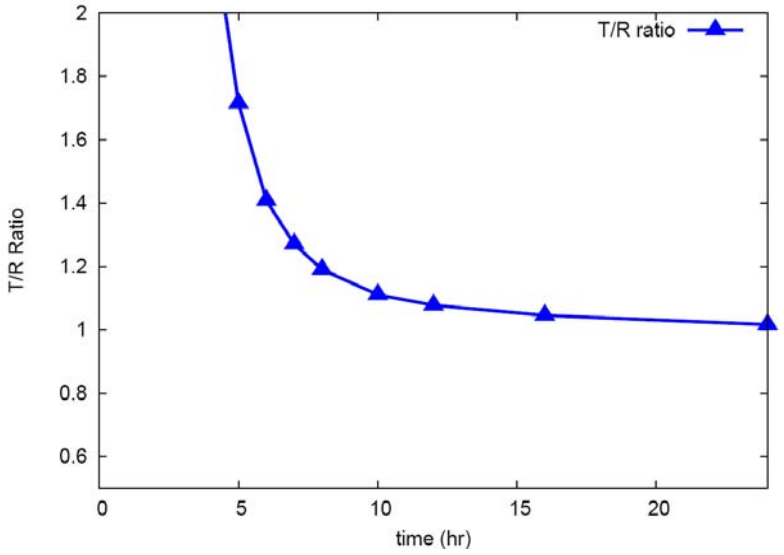
- pAUC from 0 to where?
  - The reference product T_{max} observed in the study;
  - The T_{max} of an approved IR formulation;
  - The T_{max} of an approved IR formulation plus 2 standard deviations.
- Data Analysis: 95 BE studies on MR products were analyzed for pAUC and other profile comparison measures. All studies passed Cmax and AUC

Results

- AUCpR (pAUC(0-T_{max})) sensitivity
  - All NDA BE studies have PE in 80-125%
  - 23% of ANDA BE studies have PE outside of 80-125%
  - 41% of ANDA BE studies have 90% CI outside of 80-125%
- AUCpR reasonable for most profiles
  - Exact choice not that important
- AUCpR not optimal for all
  - Multiple peaks
  - IR/ER combinations

For Different Profiles Exact pAUC Choice Does not Matter

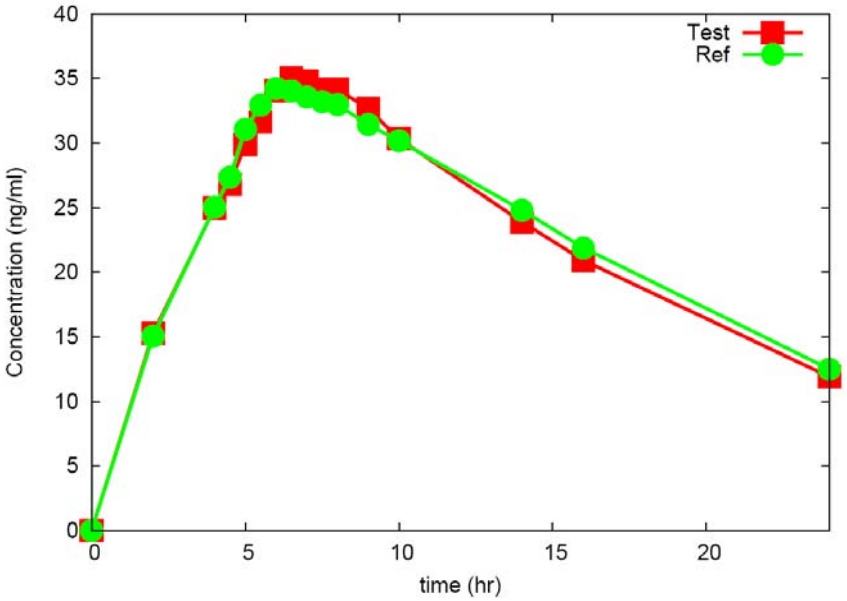


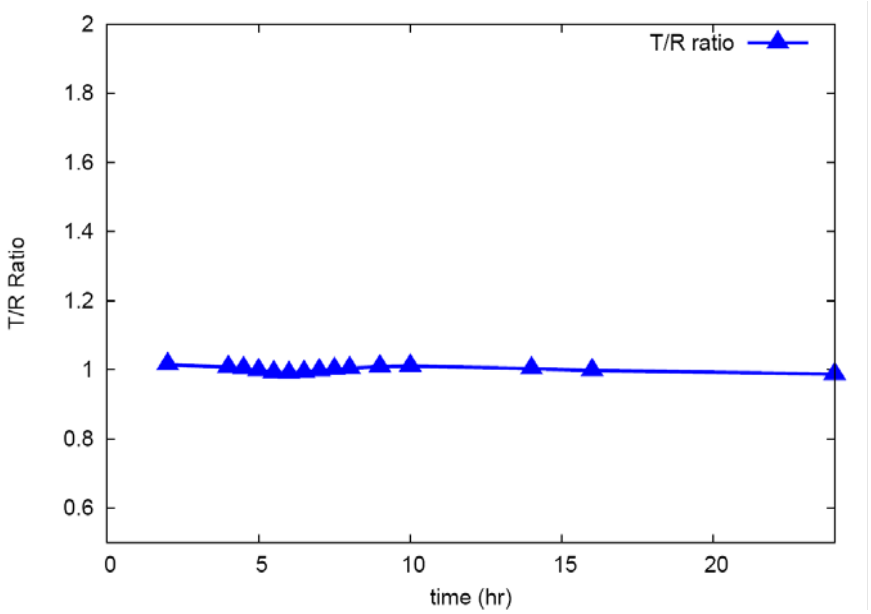


Median T_{max} Ref : 5.0
Median T_{max} Test : 3.0

All early pAUC fail
Characteristic of T and R with different lag times or IR components

For Similar Profiles Exact pAUC Choice Does not Matter

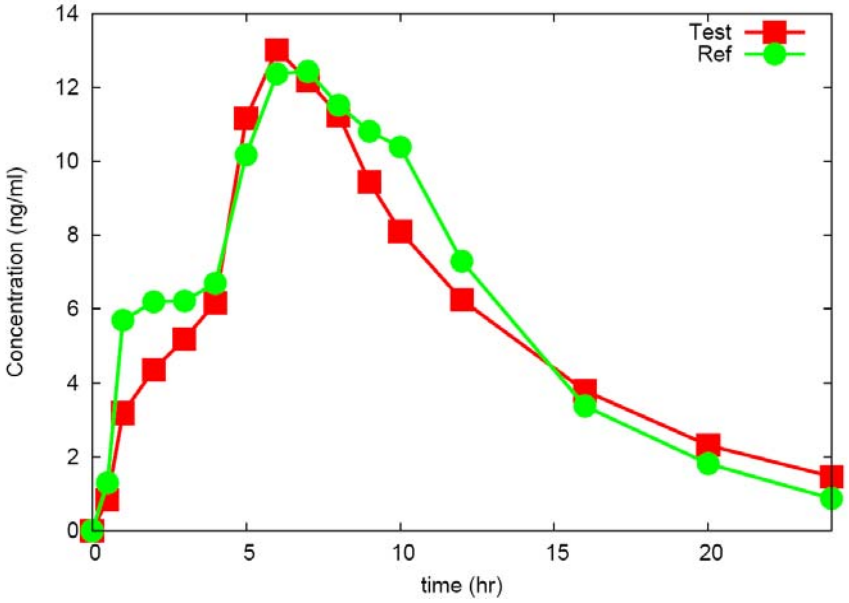


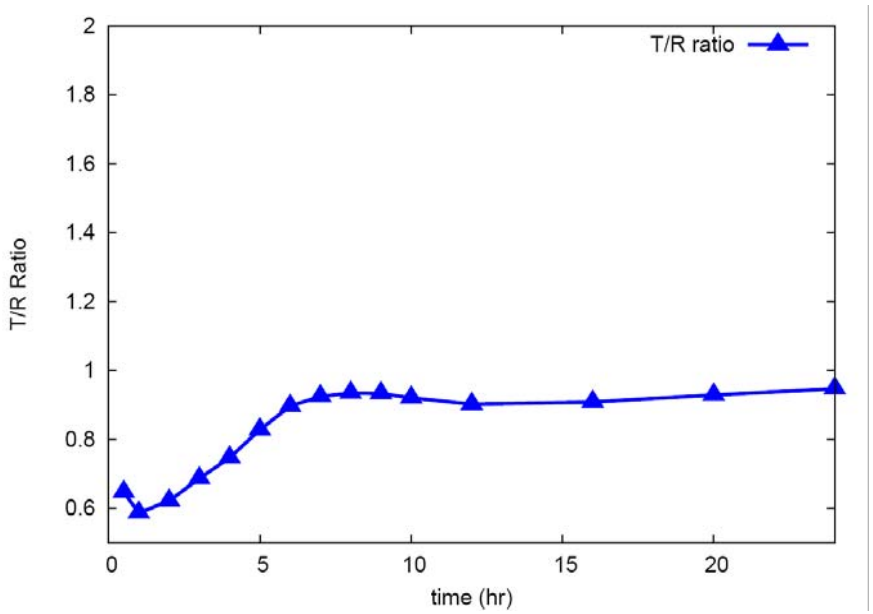


Median T_{max} Ref : 6.5
Median T_{max} Test : 6.5

45% of ANDA BE studies have all pAUC PE within 80-125%
(for times greater than 1 hr)

IR/ER Combination

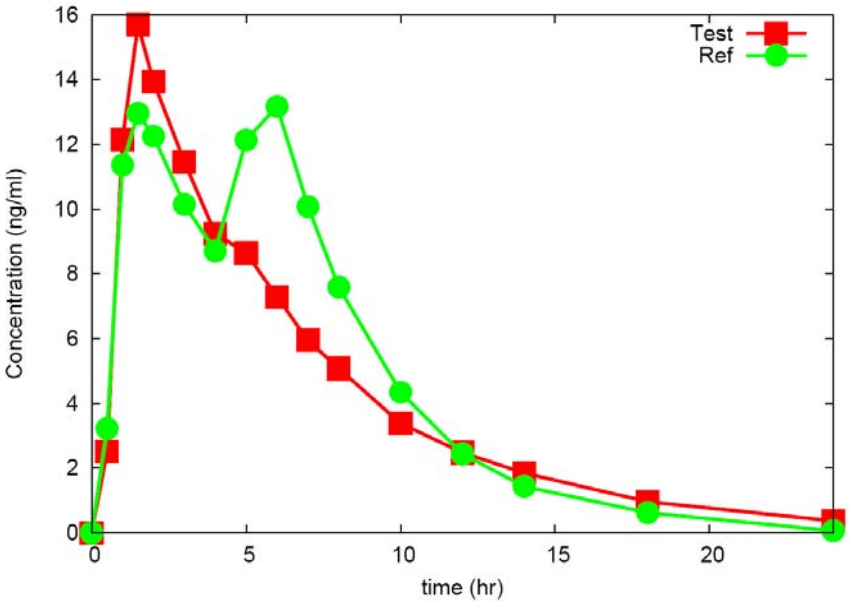


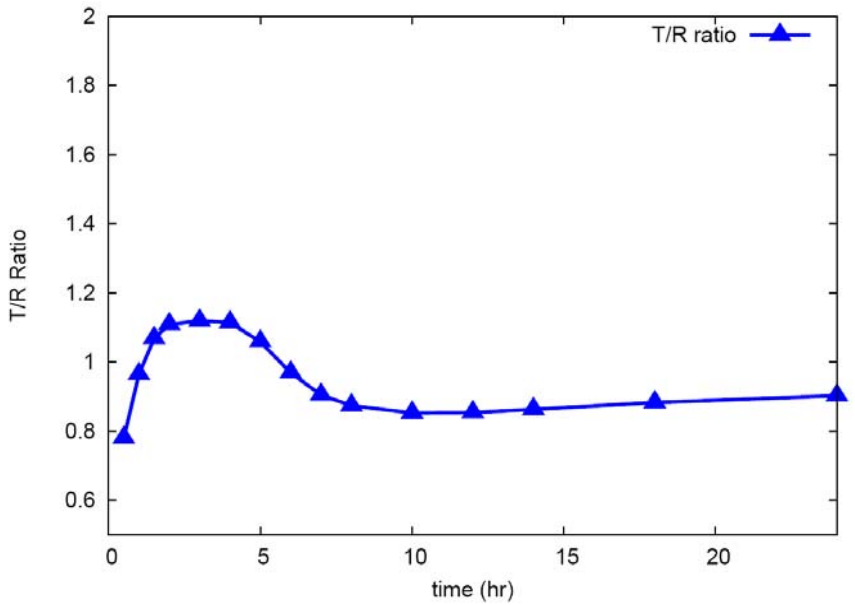


Median T_{max} Ref : 7.0
Median T_{max} Test : 6.0

Only early pAUC detect different IR component

Example Multiple Peak Confusion

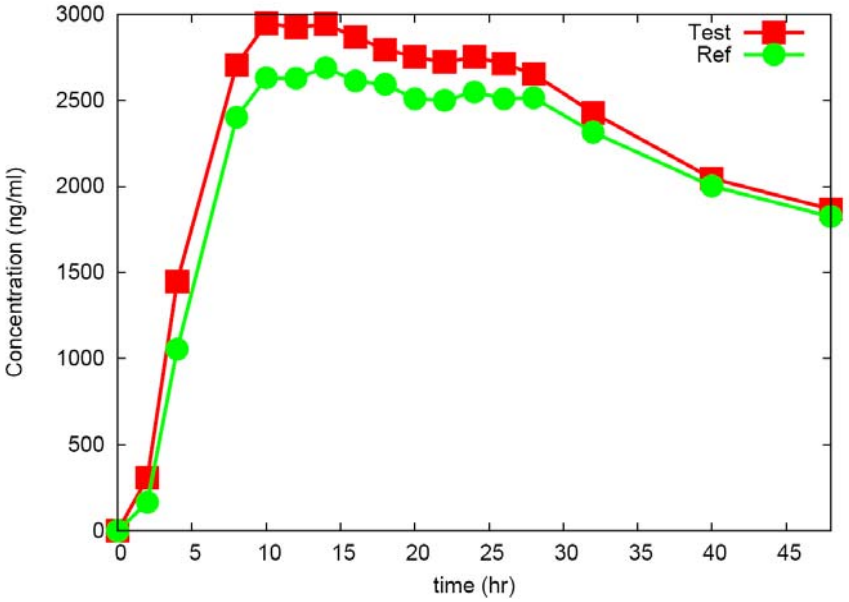


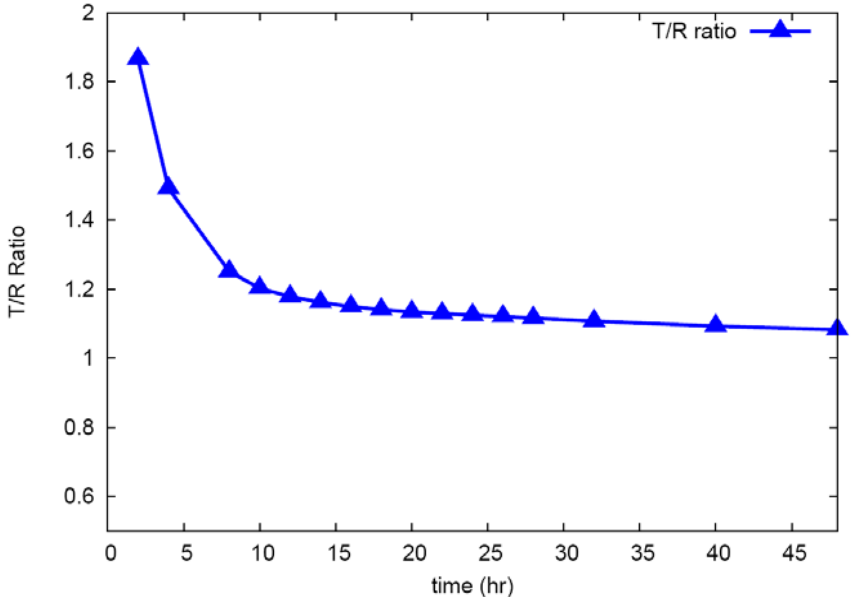


Median T_{max} Ref : 5.0
Median T_{max} Test : 1.5

All pAUC within 80-125%
Need $pAUC_{5\text{-}10}$

Example Plateau T_{max}





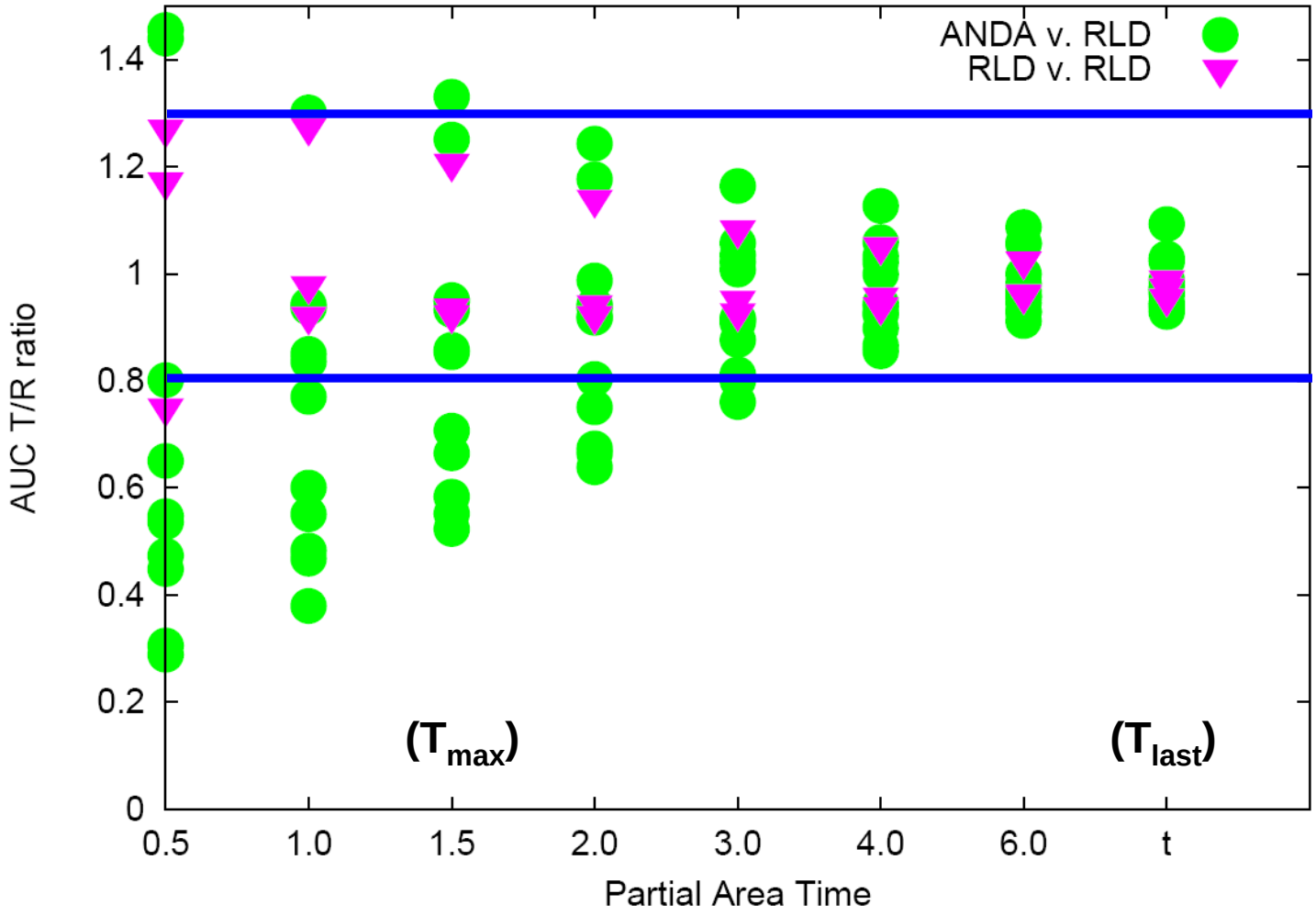
Median T_{max} Ref : 14
Median T_{max} Test : 12

pAUC very sensitive to small differences on the rising part of the curve
pAUC ratio similar across the plateau

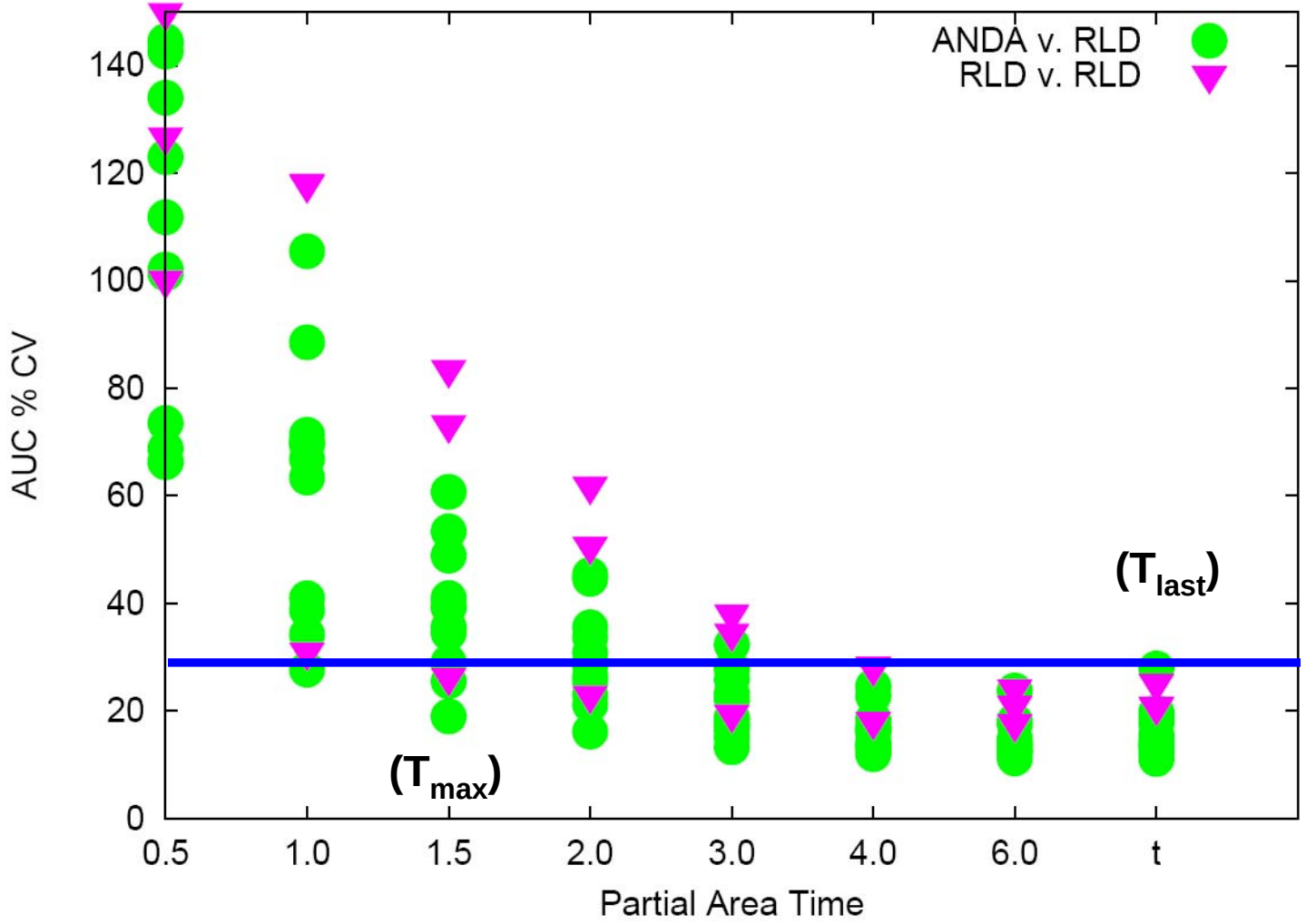
pAUC Issues

- Variability
  - As partial area time decreases variability increases
  - When partial area time is greater than 3 hours variability is reasonable for most products
- Location of sampling times
  - Retrospective analysis interpolates
  - Sampling time deviation
- Missing data
  - At early times subject has no reported concentration in the interval (Exclude)

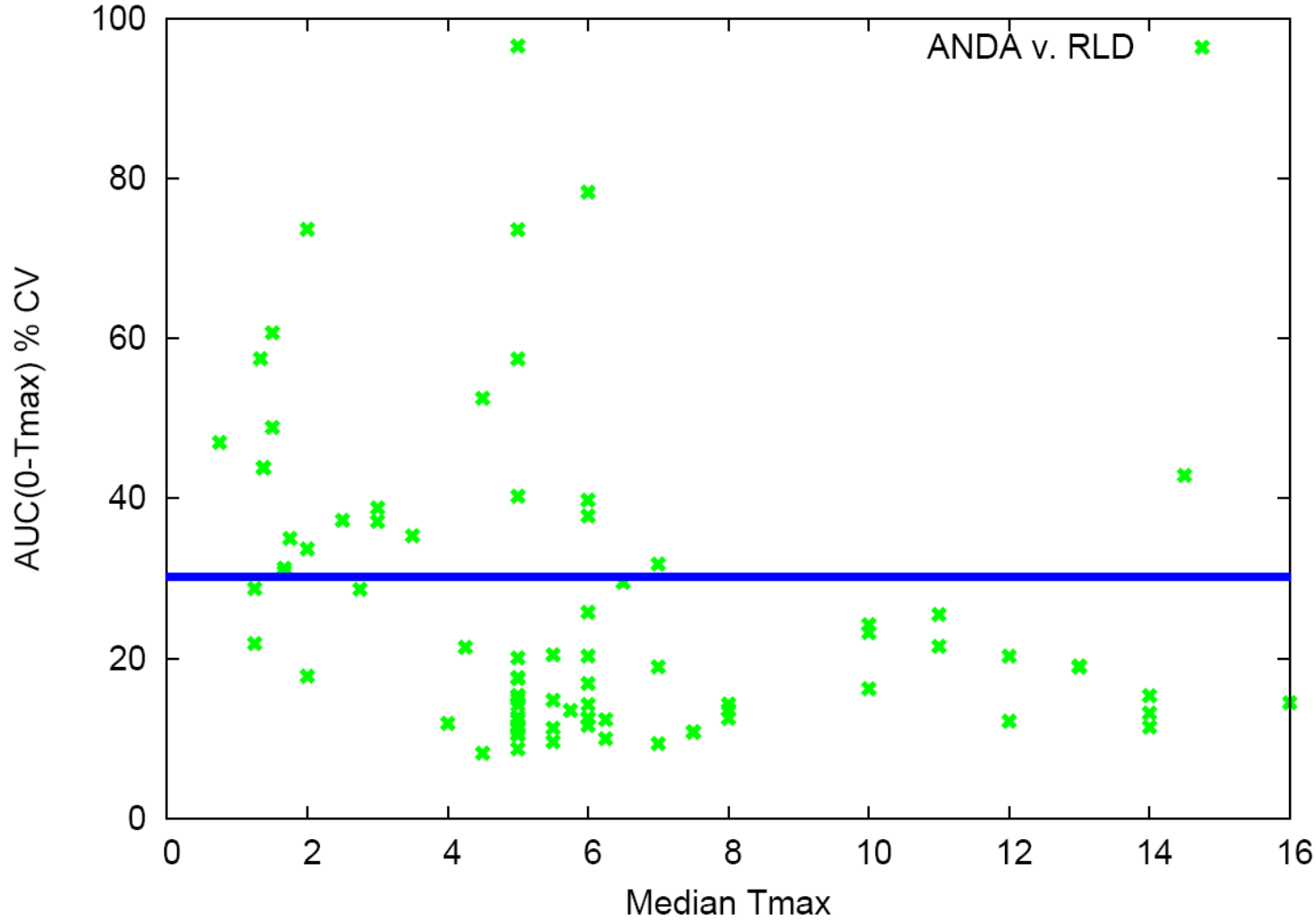
Product Discrimination via Early Exposure Metrics



Variability of Early Exposure Metrics



Variability of Early Exposure Metrics



Other pAUC Issues

- When FDA recommends pAUC(0-T)[1], FDA also recommends pAUC(T-t)
  - If pAUC(0-T) and pAUC(T-t) are equivalent then AUC(0-t) also is
- All 95 studies have pAUC(T_{max}-t) point estimate within 80-125%
- Early pAUC represents a small fraction of total area
  - But they represent a higher fraction of total absorption

[1] T is a product specific time, t is the last sampling time

How Should Profile Comparison Be Used in Product Evaluation?

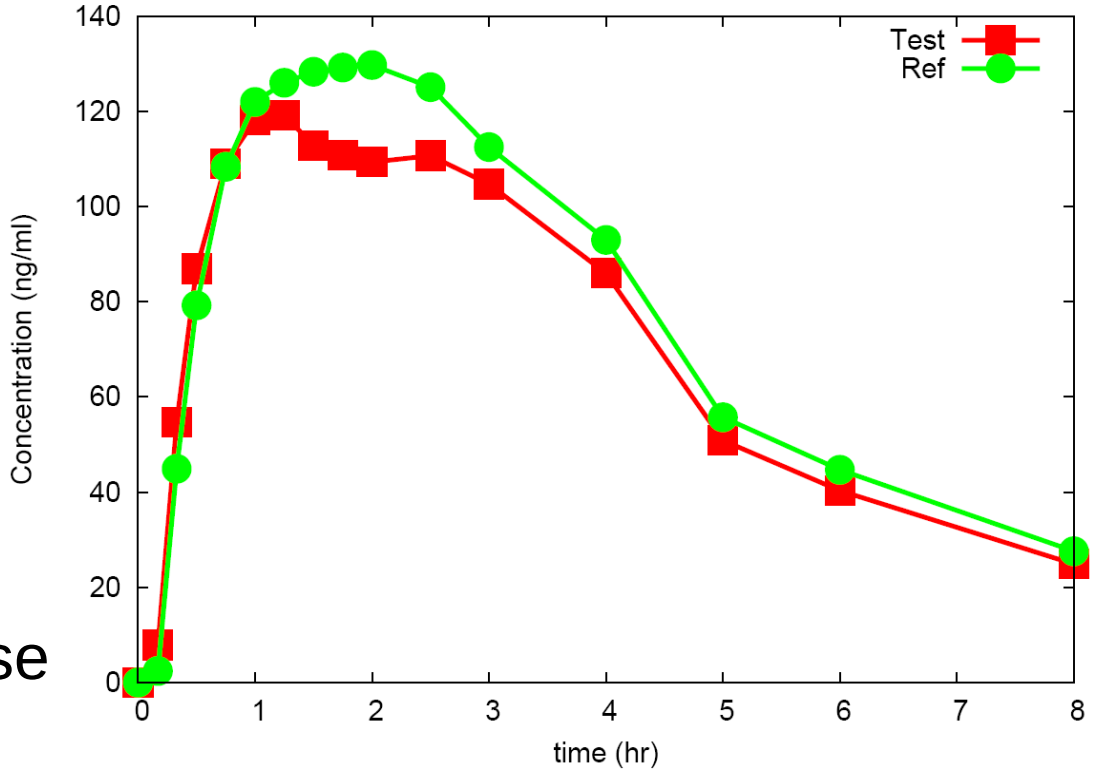
- ANDA sponsor should design their products to be equivalent to the RLD release profile
- The level of in vivo evidence recommended to demonstrate bioequivalence should be related to the potential differences **(Risk Factors)** between test and reference products.

Potential Risk Factors

- A difference in dissolution (f2 < 50) between RLD and generic products
- A difference in the ratio of extended release (ER) to IR components between RLD and generic products
- A difference in mechanism of release between RLD and generic (for example ER matrix vs. rate controlling coating)
- The drug product contains a Critical Dose Drug

PK Profile Comparison May Mitigate Concerns

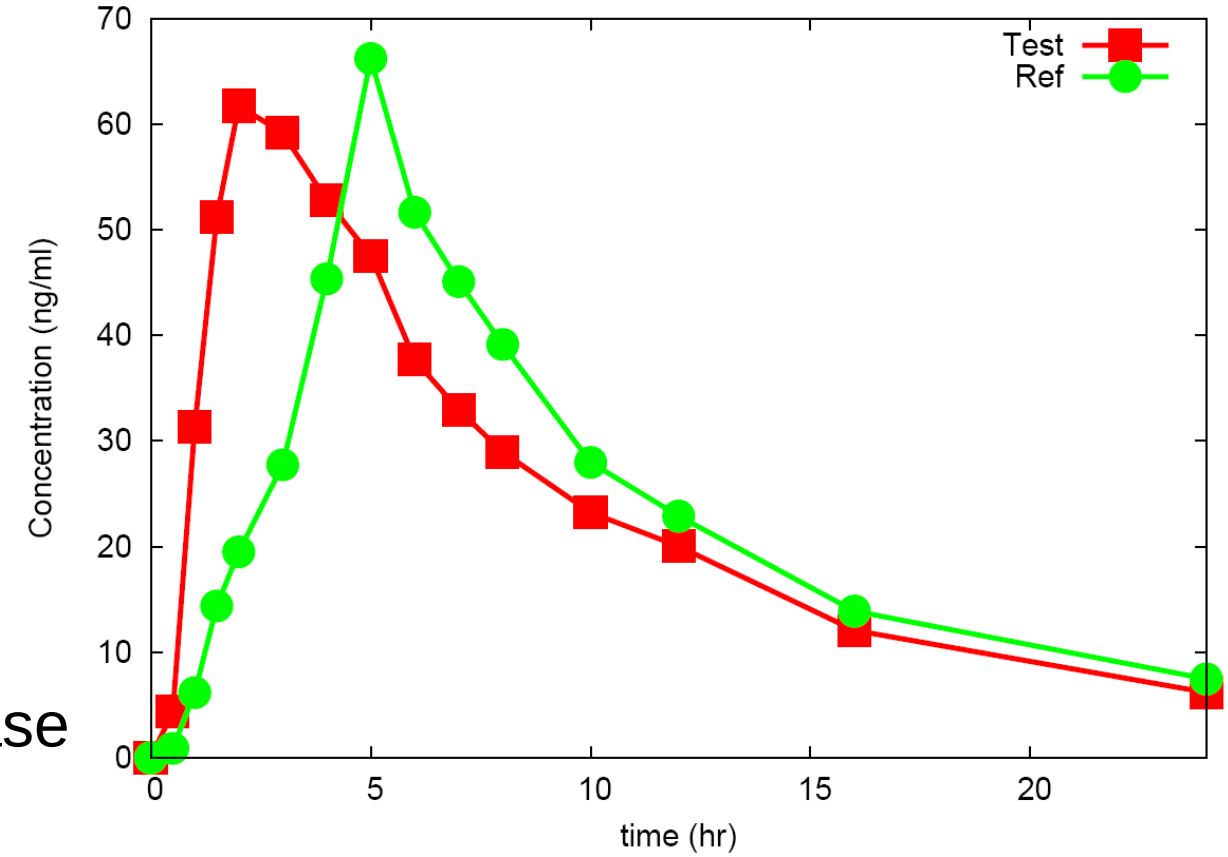
- A difference in dissolution as a function of pH
- **A difference in the ratio of extended release (ER) to IR components**
- A difference in mechanism of release



pAUC(0-1.5) ratio 0.95 (0.81-1.11)

PK Profile Comparison May Reinforce Concerns

- **A difference in dissolution as a function of pH**
- A difference in the ratio of extended release (ER) to IR components
- A difference in mechanism of release



pAUC ratio 2.12 (1.71-2.62)

Potential Use of Profile Comparison

- Routinely evaluate pAUC profile for all MR ANDA
- Supplement qualitative T_{max} analysis with quantitative comparison of pAUC (to T_{max} or critical value)
- In presence of risk factors
  - 90% CI outside of 80-125% needs clinical consult and review of mitigating factors
- In absence of risk factors
  - Point estimate outside of 80-125% needs clinical consult or review of mitigating factors
- Burden on the ANDA sponsor to demonstrate that profile differences will not affect safety or efficacy

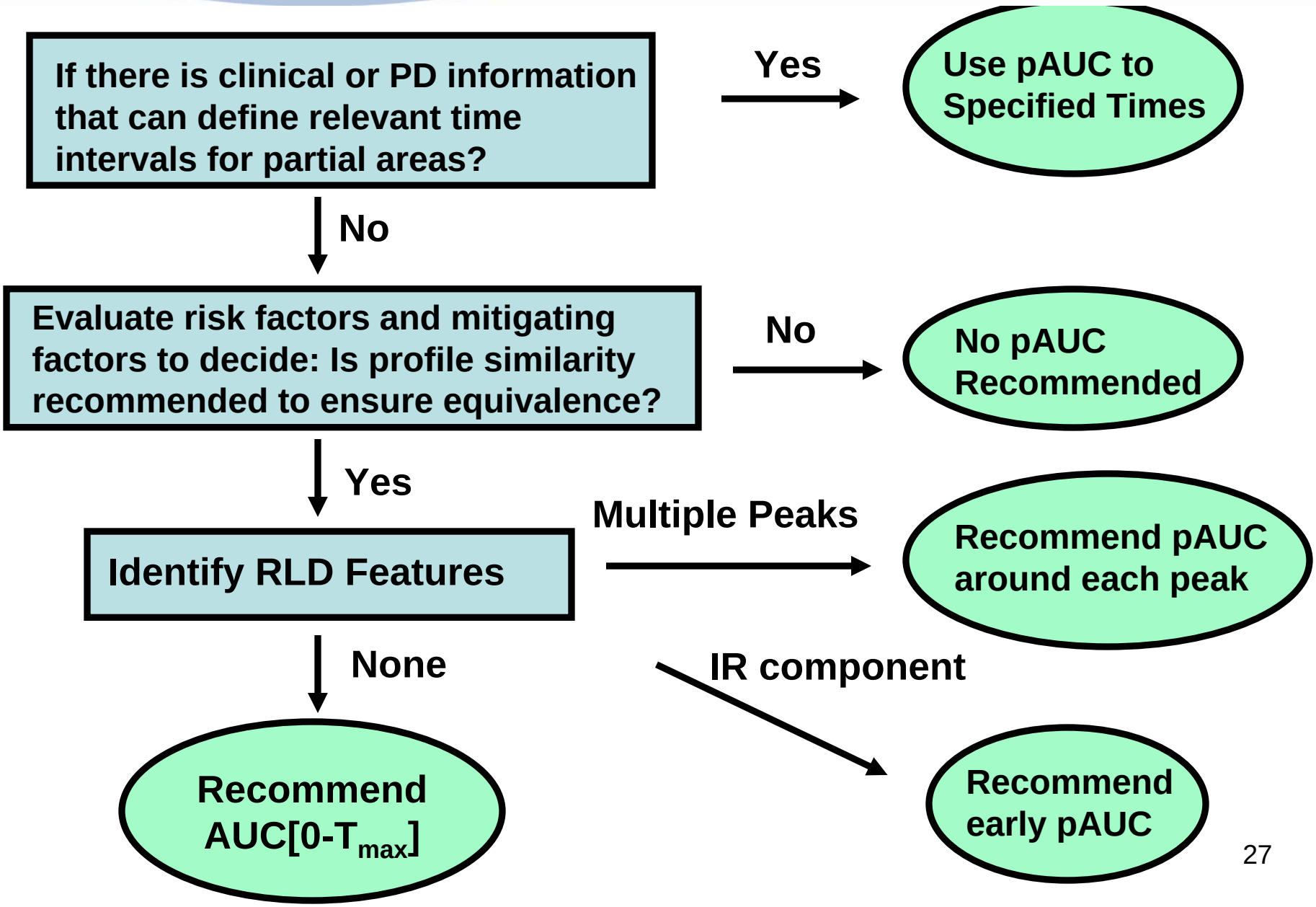
ACPS-CP Questions

April 13, 2010 – Topic 2

Use of Partial Area Under the Curve (AUC) for Products with a Complex Pharmacokinetic (PK) Profile

1. FDA is considering the use of partial AUC for these products. Please comment on our suggestion and the use of pAUC/profile comparison as a potential general tool to evaluate the significance of test to reference formulation differences.

2. Are there other profile comparison metrics that FDA should consider? We want to identify a metric that will give sponsors and reviewers clarity about when to evaluate the clinical impact of profile differences.


If there is clinical or PD information that can define relevant time intervals for partial areas?
Yes
Use pAUC to Specified Times
No
Evaluate risk factors and mitigating factors to decide: Is profile similarity recommended to ensure equivalence?
No
No pAUC Recommended
Yes
Identify RLD Features
Multiple Peaks
Recommend pAUC around each peak
None
IR component
Recommend AUC[0-Tmax]
Recommend early pAUC

Use of Partial AUC: Case Studies and BE Approaches

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence 2
Office of Generic Drugs
OPS/CDER/FDA

Pharmaceutical Science Advisory Committee Meeting
April 13, 2010

Agenda

- Current FDA acceptance criteria for bioequivalence (BE) studies
- FDA proposal for partial AUC (pAUC) metrics for multiphasic modified-release (MR) formulations of certain drugs
- Two case studies
- Summary and conclusions

Current FDA Acceptance Criteria for BE Studies

How to show that two drugs are bioequivalent

- FDA's regulations define BE as lack of a significant difference in rate and extent to which drug becomes available at the site of action
- For systemically active drugs
  - C_{max} used to determine rate of absorption
  - AUC used to determine extent of absorption

Current acceptance criteria for BE studies

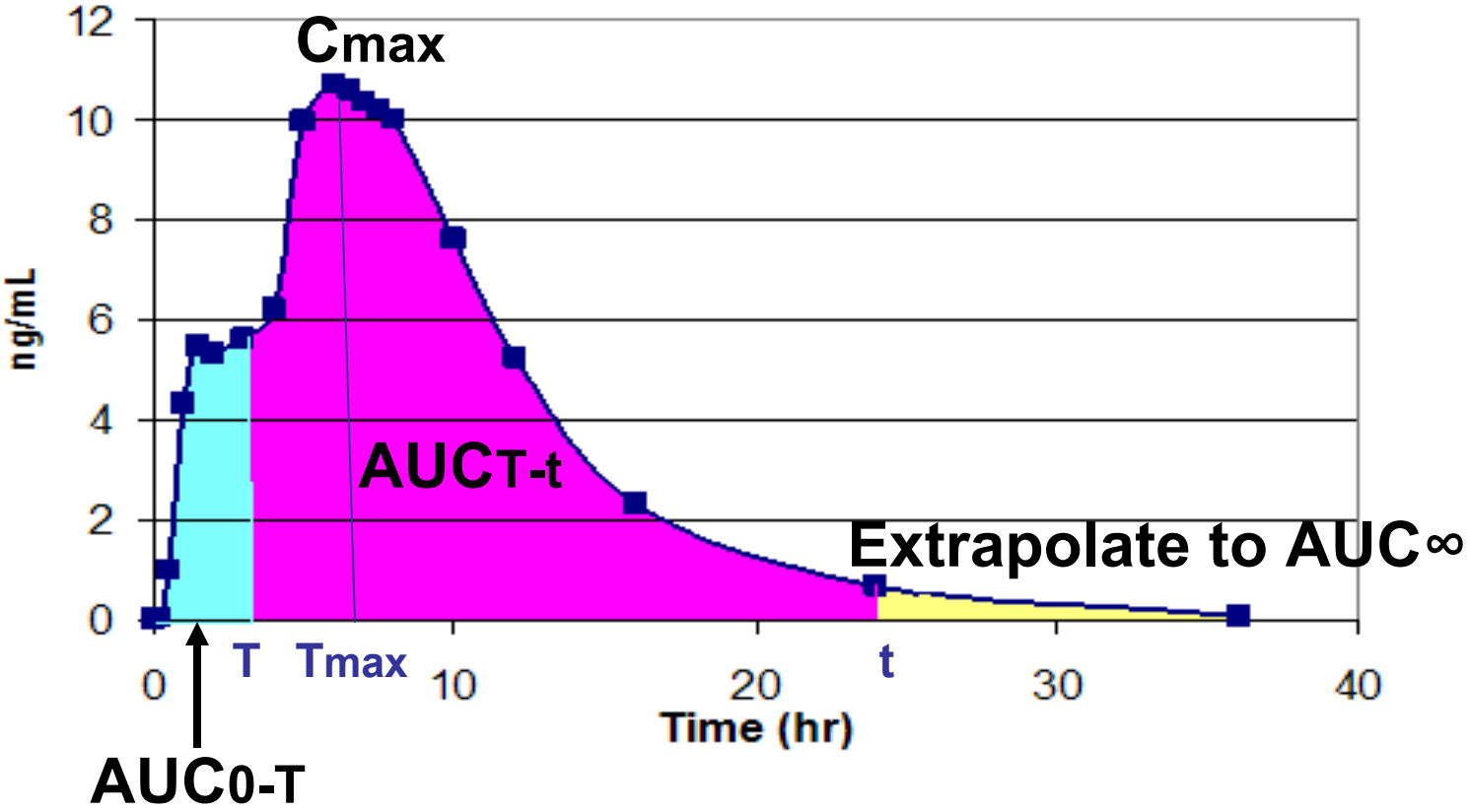
- The 90% confidence intervals of the geometric mean test/reference (T/R) C_{max} and AUC ratios should fall within the limits of 80-125%
  - Metrics are C_{max} AUC_{0-t} $AUC\infty$
- We also evaluate T_{max} qualitatively (not statistically) to compare T & R absorption rates
  - Not a continuous variable
  - Value determined by sampling times

FDA Proposal for pAUC BE Metrics for Multiphasic MR Formulations of Certain Drugs

FDA proposes to use pAUC for some specialized dosage forms

- For multiphasic MR products comprised of immediate-release (IR) and delayed-release (DR) and/or extended release (ER) portions, where
  - The IR portion is necessary for rapid onset of activity;
  - The DR or ER portion is necessary to sustain activity; and
  - Due to dosing regimen, drug does not accumulate to steady-state

Proposed BE metrics for multiphasic MR products



Proposed BE metrics for multiphasic MR products

- Propose to use 4 metrics instead of 3
  - Present: C_{max} AUC_{0-t} $AUC\infty$
  - ***Proposed: C_{max} AUC_{0-T} AUC_{T-t} $AUC\infty$***
- AUC_{0-T} should compare T & R exposure responsible for early onset of response
- AUC_{T-t} should compare T & R exposure responsible for sustained response
- All metrics should meet BE limits (80-125)

Where T is product-specific time, t is last PK sampling time

Selection of time for calculating first pAUC for multiphasic products

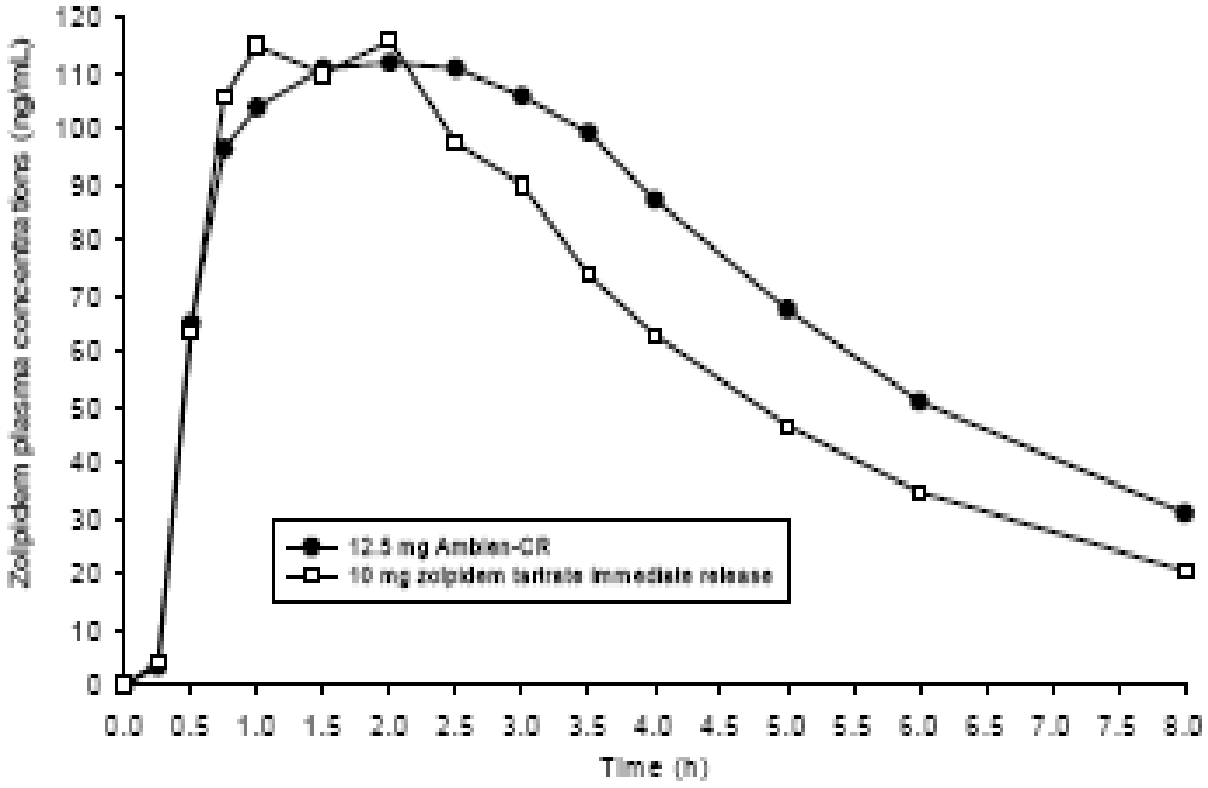
- Sampling time (T) for first pAUC is based on time at which 90-95% of subjects are likely to achieve optimal early onset of response
- Can use the T_{max} of the IR portion of the formulation to assist with determining sampling time "T"

Case Study: Zolpidem Multiphasic MR Tablet

Zolpidem MR tablet (Ambien CR®)

- Indicated for treatment of insomnia characterized by difficulties with sleep onset and/or maintenance
- A multiphasic product
  - One layer releases drug content immediately
  - Another layer allows slower release of additional drug content
- Exhibits biphasic absorption characteristics
- Given once daily, at bedtime

Mean plasma profiles
IR zolpidem bid vs Ambien CR® qd



Proposal for new BE metrics for generics to Ambien CR®

- Proposed metrics

  C_{max} $AUC_{0\text{-}1.5h}$ $AUC_{1.5h\text{-}t}$ AUC_{∞}

- Analysis focused on observations that Ambien CR®
  - Produces sleep onset at a rate equivalent to IR zolpidem tartrate;
  - Has improved sleep maintenance compared to IR zopidem tartrate; and
  - Does not cause residual effects in patients

Proposal for new BE metrics for generics to Ambien CR®

- Ambien CR® pharmacodynamic (PD) and clinical data were available to agency
- Estimated zolpidem pharmacokinetic (PK) profiles using in vitro-in vivo correlations (IVIVC), deconvolution, and simulation approaches
- $AUC_{0\text{-}1.5h}$ best at discriminating between formulations
  - By 1.5 hours, at least 90% of subjects asleep
- $AUC_{1.5h\text{-}t}$ will be used to compare T & R exposure to ensure that sleep is sustained

Proposal for new BE metrics for generics to Ambien CR®

- Simulated power curves showed that a two-way crossover BE study may need to use as many as 100 subjects to determine whether T & R have equivalent $AUC_{0\text{-}1.5h}$
- Can reduce number of study subjects using alternative approaches
  - Replicate study designs
  - Reference-scaled average bioequivalence

Is pAUC a suitable metric for fed BE studies of generics to Ambien CR®?

- Generally, FDA requests fasting and fed BE studies for all MR drug products
- An additional metric for early exposure not necessary for fed BE studies
  - For fed BE studies, use 3 traditional BE metrics (C_{max} AUC_{0-t} $AUC\infty$)
- Food delays Ambien CR® absorption
  - Label recommends administering on an empty stomach

Case Study: Methylphenidate (MPH) Multiphasic MR Products

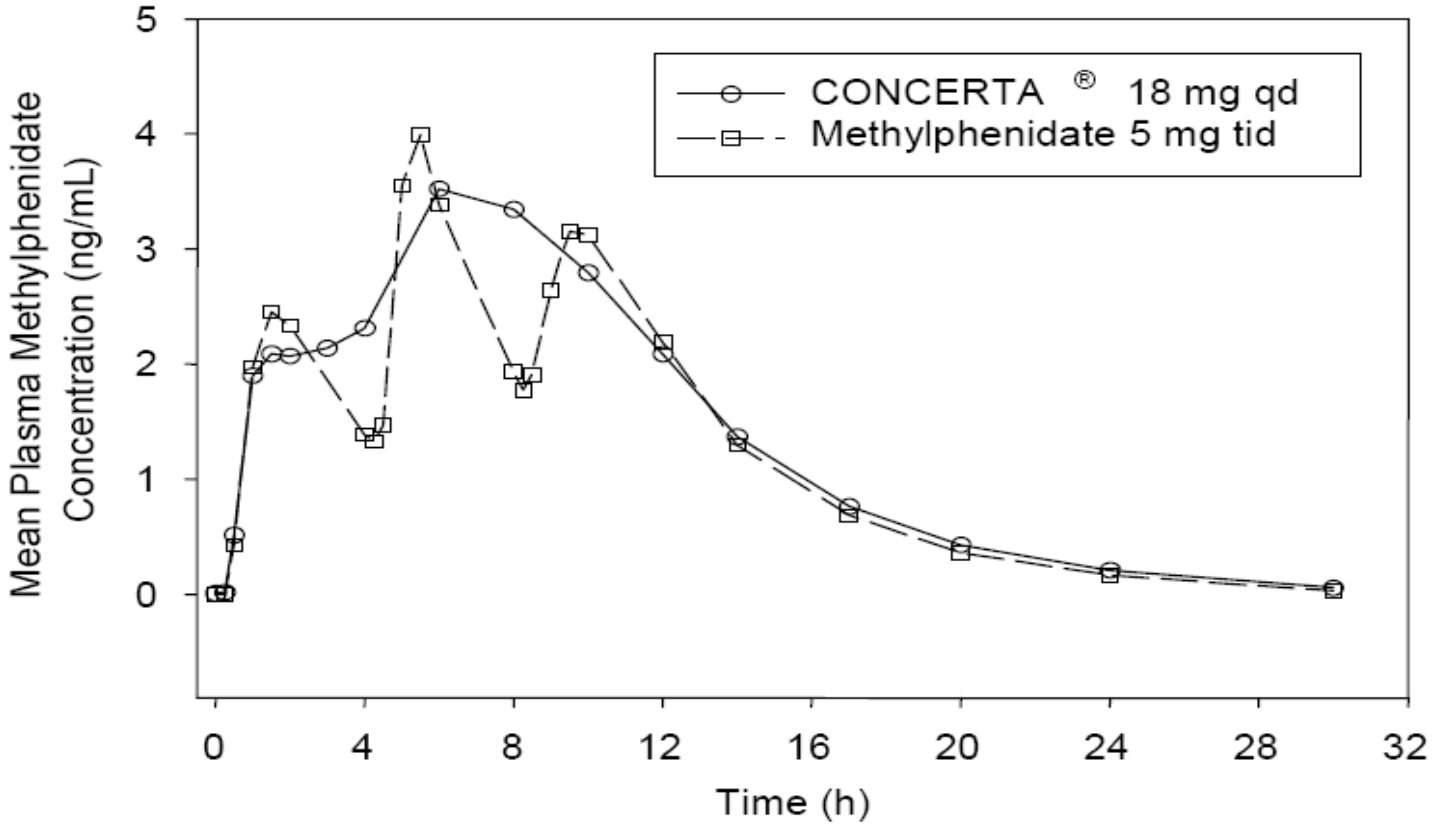
MPH multiphasic MR products

- Indicated for treatment of attention deficit disorder (ADD)
- MPH is thought block reuptake of dopamine & norephineprine into presynaptic neuron thereby increasing release into extraneuroal space
- Multiphasic formulations thought to prevent occurrence of acute tolerance

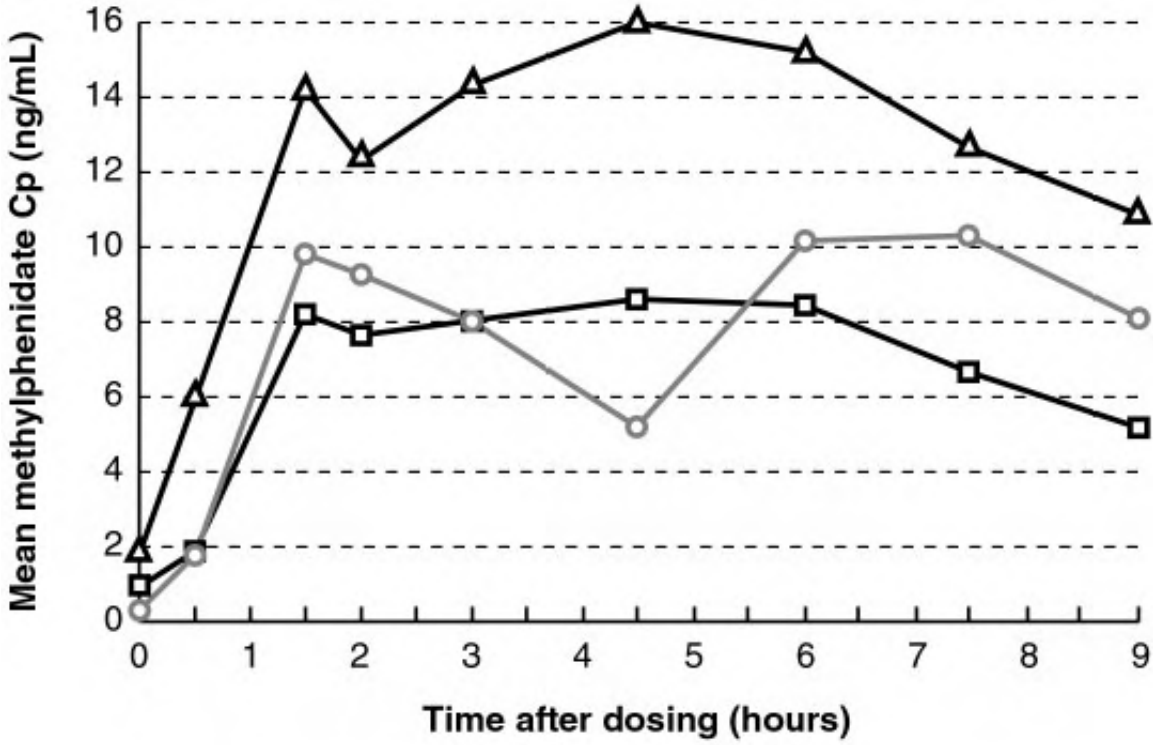
Marketed MPH multiphasic MR products

- Concerta® tablet
  - ER core with an IR overcoat
- Metadate CD® capsule
  - Formulated as 30% IR, 70% ER
- Ritalin LA® capsule
  - ½ dose as IR beads
  - ½ dose as enteric-coated, DR beads

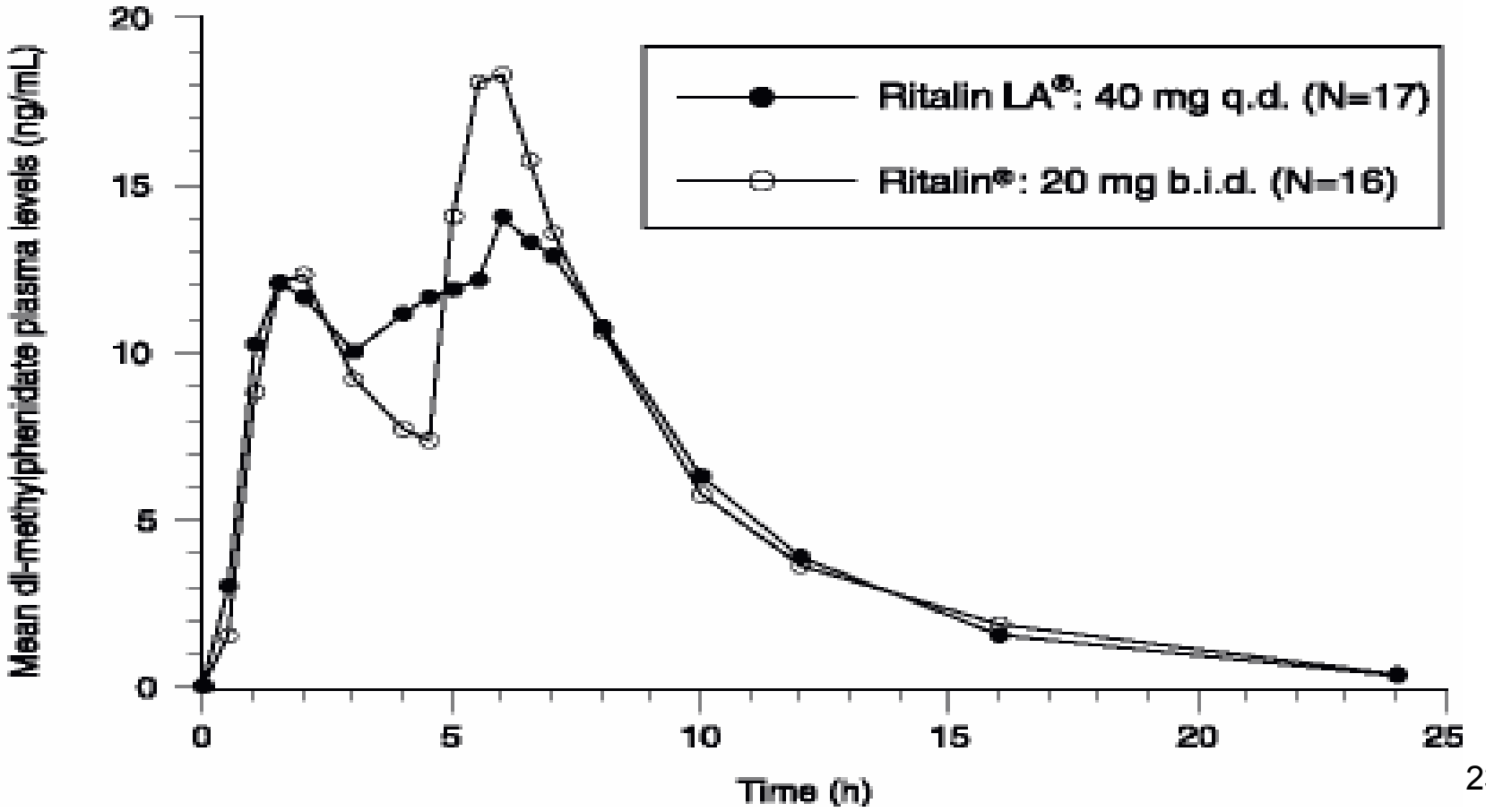
Mean plasma profiles Concerta® qd vs IR MPH tid



Mean plasma profiles Metadate CD® qd vs IR MPH bid



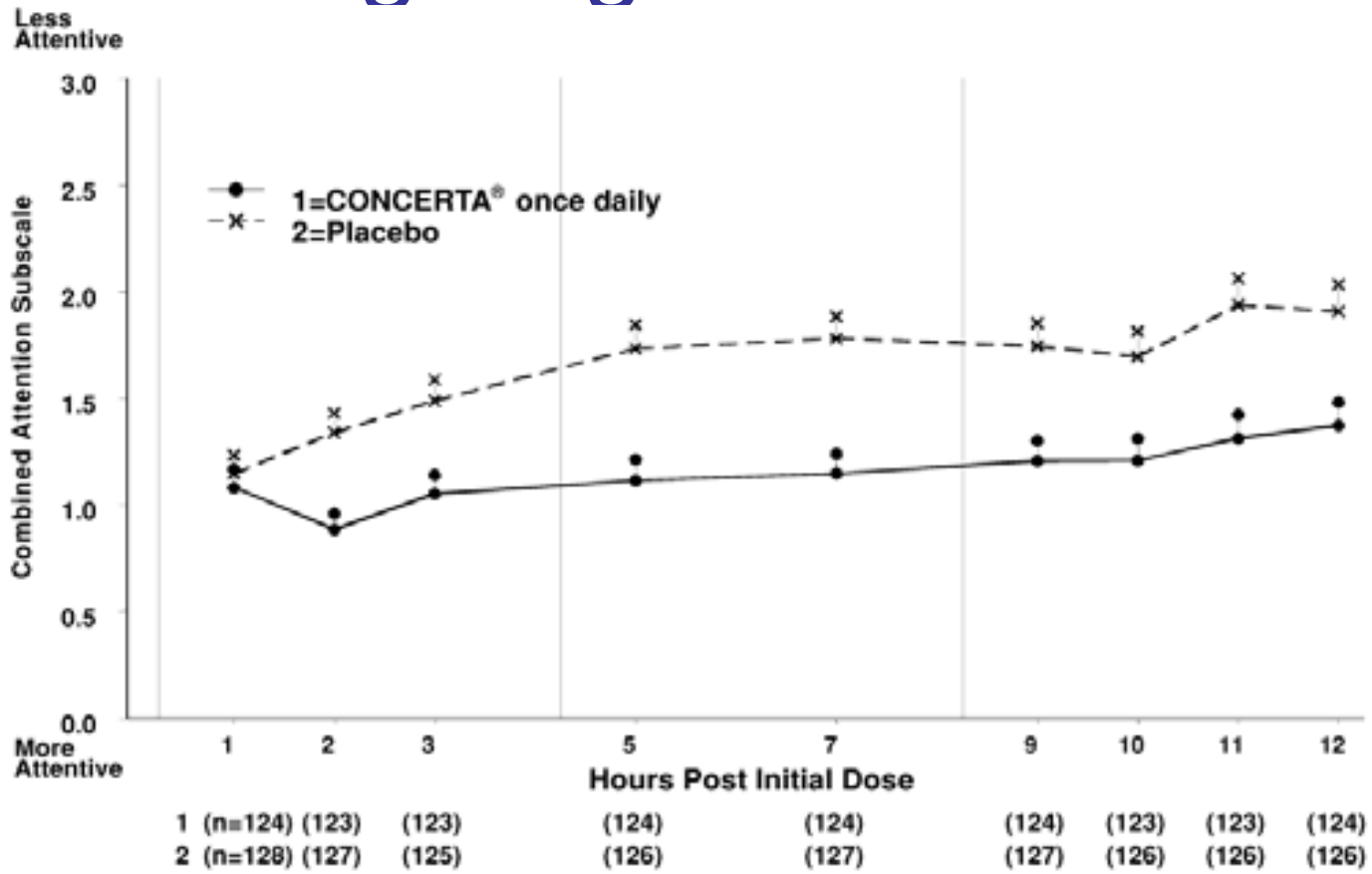
Mean plasma profiles
Ritalin LA® qd vs IR MPH bid



MPH multiphasic MR products

- Given once daily, in the morning
- MPH does not accumulate to steady-state
- Clinical outcome assessed by standardized ADD symptom rating scores
  - Score data are suitable for PD modeling
- PK / PD models show that peak response achieved at about same time as peak MPH plasma concentrations
- For Concerta®, maximal response occurs 2 hr post-dosing, sustained throughout day

Clinical response throughout day following single Concerta® dose



Note: Mean and mean plus standard error of mean shown

Proposal for pAUC BE metrics for generics to MPH multiphasic products

- For fasting BE studies

  C_{max} $AUC_{0\text{-}3h}$ $AUC_{3h\text{-}t}$ $AUC\infty$

- For fed BE studies

  C_{max} $AUC_{0\text{-}4h}$ $AUC_{4h\text{-}t}$ $AUC\infty$

- Early pAUC should compare T & R exposure associated with response onset
- Later pAUC should compare T & R exposure associated with sustained response

Using $AUC_{0\text{-}3h}$ for BE studies of generics to MPH multiphasic products

- In fasting subjects
  - The IR MPH T_{max} [mean ± S.D.] is 2 ± 0.5 h;
- 2 hr is also time at which maximal response [compared to placebo] is achieved;
- By 3 hr, expect that 95% of patients should achieve maximal early onset of response
  - Mean ± 2 S.D. = 95% of population response
  - 95% of subjects should achieve maximal early onset of response by 2 h + [2 x 0.5 h] = 3 h

Using $AUC_{0\text{-}4h}$ for fed BE studies of generics to MPH multiphasic products

- Food delays IR MPH absorption by about one (1) hour
  - T_{max} [Mean ± S.D.] = 3 ± 0.5 h
- By 4 hours, expect that 95% of subjects should achieve optimal early onset of response if MPH is taken with food

Using AUC_{3h-t} & AUC_{4h-t} for BE of generics to MPH multiphasic products

The metrics AUC_{3h-t} (fasting) and AUC_{4h-t} (fed) should ensure that T & R exposure is same during period when response should be sustained

Summary and Conclusions

Summary and Conclusions

- Present FDA BE study acceptance criteria may not be adequate for some drugs formulated as multiphasic MR products
- FDA proposes using two pAUCs for BE studies of multiphasic MR products formulated to achieve rapid onset of response and sustained response
  - The first pAUC will compare T & R early exposure
  - The second pAUC will compare T& R later exposure

Summary and Conclusions

- FDA proposes selecting the sampling time for the first pAUC to ensure that 90-95% of subjects will have achieved the optimal early onset of response
- The objective is to ensure that the proposed generic to a multiphasic MR product, once approved, will be switchable with its corresponding reference

ACPS-CP Questions

April 13, 2010 – Topic 2

Use of Partial Area Under the Curve (AUC) for Products with a Complex Pharmacokinetic (PK) Profile

1. FDA is considering the use of partial AUC for these products. Please comment on our suggestion and the use of pAUC/profile comparison as a potential general tool to evaluate the significance of test to reference formulation differences.

2. Are there other profile comparison metrics that FDA should consider? We want to identify a metric that will give sponsors and reviewers clarity about when to evaluate the clinical impact of profile differences.